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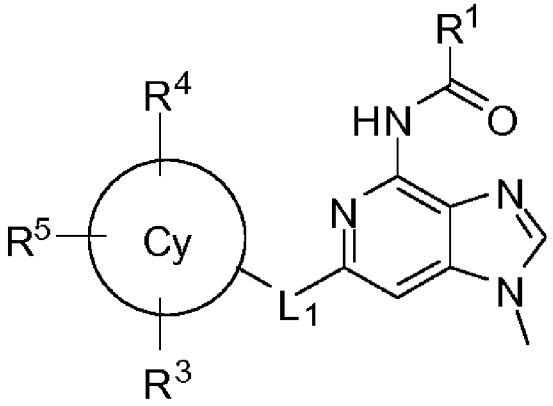
(54) **Title**: NOVEL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS



I

(57) **Abstract**: The present invention discloses compounds according to Formula (I), wherein R^1, R^3, R^4, R^5, L1, and Cy are as defined herein. The present invention also provides compounds, methods for the production of said compounds of the invention, pharmaceutical compositions comprising the same and their use in allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons. The present invention also methods for the prevention and/or treatment of the aforementioned diseases by administering a compound of the invention.

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NOVEL COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS.

FIELD OF THE INVENTION

[0001] The present invention relates to compounds and their use in allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons. In particular, the compounds of the invention may inhibit JAK, a family of tyrosine kinases, more particularly JAK1 and/or TYK2. The present invention also provides methods for the production of the compounds of the invention, pharmaceutical compositions comprising the compounds of the invention, methods for the prevention and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0002] Janus kinases (JAKs) are cytoplasmic tyrosine kinases that transduce cytokine signaling from membrane receptors to STAT transcription factors. Four JAK family members are described, JAK1, JAK2, JAK3 and TYK2. Upon binding of the cytokine to its receptor, JAK family members auto- and/or transphosphorylate each other, followed by phosphorylation of STATs that then migrate to the nucleus to modulate transcription. JAK-STAT intracellular signal transduction serves the interferons, most interleukins, as well as a variety of cytokines and endocrine factors such as EPO, TPO, GH, OSM, LIF, CNTF, GM-CSF and PRL (Vainchenker et al., 2008).

[0003] The combination of genetic models and small molecule JAK inhibitor research revealed the therapeutic potential of several JAKs.

[0004] JAK1 is a target in the immuno-inflammatory disease area. JAK1 heterodimerizes with the other JAKs to transduce cytokine-driven pro-inflammatory signaling. Therefore, inhibition of JAK1 is of interest for immuno-inflammatory diseases with pathology-associated cytokines that use JAK1 signaling, such as IL-6, IL-4, IL-5, IL-12, IL-13, IL-23, or IFNγ, as well as for other diseases driven by JAK-mediated signal transduction.

[0005] JAK1 and JAK2 are implicated in intracellular signal transduction for many cytokines and hormones. Pathologies associated with any of these cytokines and hormones can be ameliorated by JAK1 and JAK2 inhibitors. Hence, several allergy, inflammation and autoimmune disorders might benefit from treatment with compounds described in this invention including rheumatoid arthritis, systemic lupus erythematosis, juvenile idiopathic arthritis, osteoarthritis, asthma, chronic obstructive pulmonary disease COPD, tissue fibrosis, eosinophilic inflammation, eosophagitis, inflammatory bowel diseases (*e.g.* Crohn's, ulcerative colitis), transplantation, graft-versus-host disease, psoriasis, myositis, multiple sclerosis (Kopf et al., 2010). However, side effects believed to be associated to the inhibition of JAK2

have been reported including anemia, leukopenia, thrombocytopenia, and hypercholesterolemia (O'Shea et al., 2013; O'Shea and Plenge, 2012).

[0006] JAK3 is validated by mouse and human genetics as an immune-suppression target (O'Shea et al., 2004). Nevertheless, JAK3 inhibitors were successfully taken into clinical development, initially for organ transplant rejection but later also in other immuno-inflammatory indications such as rheumathoid arthritis (RA), psoriasis and Crohn's disease (http://clinicaltrials.gov/).

[0007] TYK2 is a potential target for immuno-inflammatory diseases, being validated by human genetics and mouse knock-out studies (Levy and Loomis, 2007).

[0008] JAK family members have been implicated in additional conditions including myeloproliferative disorders (O'Sullivan et al., 2007), in cancers, in particular leukaemias e.g. acute myeloid leukaemia (O'Sullivan et al., 2007; Xiang et al., 2008) and acute lymphoblastic leukaemia (Mullighan et al., 2009) or solid tumours e.g. uterine leiomyosarcoma (Constantinescu et al., 2008), prostate cancer (Tam et al., 2007). These results indicate that inhibitors of JAK, in particular of JAK1 and/or JAK2, may also have utility in the treatment of cancers (leukaemias and solid tumours e.g. uterine leiomyosarcoma, prostate cancer).

[0009] Castleman's disease, multiple myeloma, mesangial proliferative glomerulonephritis, psoriasis, and Kaposi's sarcoma are likely due to hypersecretion of the cytokine IL-6, whose biological effects are mediated by intracellular JAK-STAT signaling (Naka et al., 2002). This result shows that inhibitors of JAK, may also find utility in the treatment of said diseases.

[0010] Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Recently, it has been found via genome-wide association (GWAS) studies that T cell protein tyrosine phosphatase (TCPTP) is a JAK/STAT and growth factor receptor phosphatase that has been linked to the pathogenesis of type 1 diabetes, rheumatoid arthritis, and Crohn's disease by GWAS (Zikherman and Weiss, 2011). Therefore, inhibition of the JAK pathway might provide a way of treating IBD.

[0011] Psoriasis is a disease that can affect the skin. The cause of psoriasis is not fully understood, however, it is believed that it is an immune mediated related disease linked to the release of cytokines, in particular TNFα, which causes inflammation and rapid reproduction of the skin cells. This hypothesis has been corroborated by the observation that immunosuppressant medication can clear psoriasis plaques (Zikherman and Weiss, 2011)

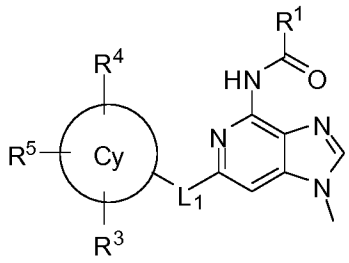
[0012] Psoriasis can also cause inflammation of the joints, which is known as psoriatic arthritis. Between 10-30% of all people with psoriasis also have psoriatic arthritis (Committee for Medicinal Products for Human Use (CHMP) (18 November 2004). "Guideline on Clinical Investigation of Medicinal Products indicated for the treatment of Psoriasis"). Because of its chronic recurrent nature, psoriasis is a challenge to treat. It has recently been demonstrated that inhibition of JAK could result in successful improvement of the psoriatic condition. (Punwani et al., 2012). In particular, recent studies have shown that JAK1 and TYK2 inhibition may be useful in the treatment of psoriasis (Works et al., 2014).

[0013] Therefore, because the current therapies are not satisfactory, there remains a need to identify further compounds that may be of use in the prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons. In order to make use of the therapeutic benefit of JAK inhibitors without also triggering side effects, it would be beneficial to develop compounds with high selectivity, in particular towards JAK1 and/or TYK2, and/or with low potency against JAK2. Moreover, to be used as a medicine, said compounds should present suitable ADME properties, in particular towards aldehyde oxidase (Pryde et al., 2010).

SUMMARY OF THE INVENTION

[0014] The present invention is based on the identification of novel compounds, and their ability to act as inhibitors of JAKs and that they may be useful for the treatment of prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons. In particular, the compounds of the invention may show selectivity towards JAK1 and TYK2, and more particularly, the compounds of the invention may show low potency against JAK2. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons by administering the compounds of the invention.

[0015] Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula (I):



I

wherein

R^1 is

– C_{3-4} cycloalkyl, optionally substituted with one or more independently selected C_{1-4} alkyl, halo, or -CN,

– $-CH_3$, $-CH_2-OH$, $-CH_2-CN$, $-CH_2-CH_2-CN$, or

– $-OCH_3$;

L_1 is $-NR^2-$; or -O-;

Cy is

– phenyl, or

– 6 membered heteroaryl comprising 1, 2 or 3 nitrogen heteroatoms;

R^2 is

– H,

– C_{1-4} alkyl optionally substituted with one or more OH,

– C_{2-4} alkenyl comprising one double bond;

R^3 is

– H,

– halo,

– C_{1-4} alkyl optionally substituted with one or more halo, or

– C_{1-4} alkoxy optionally substituted with one or more halo;

R^4 is H, or halo or C_{1-4} alkyl;

R^5 is halo, -CN, or $–L_2-R^6$, wherein

L_2 is

– a bond,

– -W-, or

– -C_{1-2} alkylene-W-;

W is -S-, -O-, -NR^7-, -C(=O)-, -C(=O)O-, -C(=O)NR^7-, -NR^7C(=O)-, -SO_2-, -SO_2NR^7-, or -NR^7SO_2-;

R^6 is

– H,

– C_{1-6} alkyl optionally substituted with one or more independently selected R^8 groups,

– C_{3-7} cycloalkyl, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– C_{6-10} aryl optionally substituted with one or more groups independently selected from R^9, or

– 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9;

or when is R^5 is $–L_2-R^6$, R^5 and R^2, together may form a fused 6 membered heterocycloalkyl ring with Cy;

R^7 is H, or C_{1-4} alkyl;

R^8 is

– -OH,

– -CN,

– halo, or

– C_{1-4} alkoxy; and

each R^9 is independently selected from

– oxo,

– halo,

– -CN,

– C_{1-4} alkyl, and

– $-SO_2-C_{1-4}$ alkyl, which alkyl is optionally substituted with one or more halo.

[0016] In a particular aspect, the compounds of the invention are provided for use in the prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.

[0017] In another particular aspect, the compound of the invention may show selectivity towards JAK1 and TYK2. More particularly, the compound of the invention may show a low potency towards JAK2 which in turn may result in good safety profiles and reduced dose limiting issues.

[0018] In another particular embodiment, the compounds of the invention show good safety and ADME properties.

[0019] In yet another further particular embodiment, the compounds of the invention unexpectedly show lower levels of metabolism by liver aldehyde oxidase compared to closely related analogues, which may result in good exposure levels and lower dosage regimen.

[0020] In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. In a particular aspect, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the invention. In a more particular aspect, the further therapeutically active ingredient is an agent for the treatment of prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.

[0021] Moreover, the compounds of the invention, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0022] In a further aspect of the invention, this invention provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the invention as described herein.

[0023] The present invention also provides pharmaceutical compositions comprising a compound of the invention, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular

aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.

[0024] In additional aspects, this invention provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.

[0025] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0026] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0027] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0028] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term "substituted" is to be defined as set out below. It should be further understood that the terms "groups" and "radicals" can be considered interchangeable when used herein.

[0029] The articles 'a' and 'an' may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example 'an analogue' means one analogue or more than one analogue.

[0030] 'Alkyl' means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl ($-CH_3$), ethyl ($-CH_2-CH_3$), n-propyl ($-CH_2-CH_2-CH_3$), isopropyl ($-CH(CH_3)_2$), n-butyl ($-CH_2-CH_2-CH_2-CH_3$), tert-butyl ($-CH_2-C(CH_3)_3$), sec-butyl ($-CH_2-CH(CH_3)_2$), n-pentyl ($-CH_2-CH_2-CH_2-CH_2-CH_3$), n-hexyl ($-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$), and 1,2-dimethylbutyl ($-CHCH_3-C(CH_3)H_2-CH_2-CH_3$). Particular alkyl groups have between 1 and 4 carbon atoms.

[0031] 'Alkenyl' refers to monovalent olefinically (unsaturated) hydrocarbon groups with the number of carbon atoms specified. Particular alkenyl has 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups include ethenyl ($-CH=CH_2$), n-propenyl ($-CH_2CH=CH_2$), isopropenyl ($-C(CH_3)=CH_2$) and the like.

[0032] 'Alkylene' refers to divalent alkene radical groups having the number of carbon atoms specified, in particular having 1 to 6 carbon atoms and more particularly 1 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), or $-CH(CH_3)-$ and the like.

[0033] 'Alkoxy' refers to the group O-alkyl, where the alkyl group has the number of carbon atoms specified. In particular the term refers to the group $-O-C_{1-6}$ alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0034] 'Amino' refers to the radical $-NH_2$.

[0035] 'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, monocyclic or fused polycyclic, with the number of ring atoms specified. Specifically, the term includes groups that include from 6 to 10 ring members. Particular aryl groups include phenyl, and naphthyl.

[0036] 'Cycloalkyl'refers to a non-aromatic hydrocarbyl ring structure, monocyclic, fused polycyclic, bridged polycyclic, or spirocyclic, with the number of ring atoms specified. A cycloalkyl may have from 3 to 12 carbon atoms, in particular from 3 to 10, and more particularly from 3 to 7 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0037] 'Cyano' refers to the radical -CN.

[0038] 'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

[0039] 'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.* heteroalkyl, cycloalkyl, *e.g.* heterocycloalkyl, aryl, *e.g.* heteroaryl, and the like having from 1 to 4, and particularly from 1, 2, or 3 heteroatoms, more typically 1 or 2 heteroatoms, for example a single heteroatom.

[0040] 'Heteroaryl' means an aromatic ring structure, monocyclic or fused polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. In particular, the aromatic ring structure may have from 5 to 9 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a fused bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can

be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

[0041] Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrolyl, furanyl, thiophenyl, imidazolyl, furazanyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl and tetrazolyl groups.

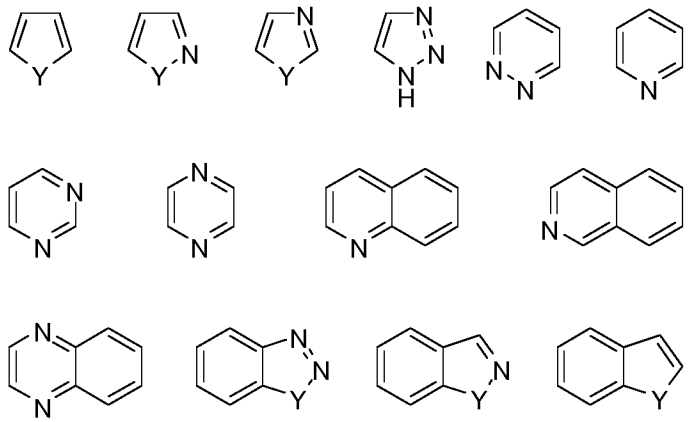
[0042] Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl and triazinyl.

[0043] Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five-membered ring include but are not limited to imidazothiazolyl and imidazoimidazolyl.

[0044] Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuranyl, benzothiophenyl, benzoimidazolyl, benzoxazolyl, isobenzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, isobenzofuranyl, indolyl, isoindolyl, indolizinyl, purinyl (*e.g.* adenine, guanine), indazolyl, pyrazolopyrimidinyl, triazolopyrimidinyl, and pyrazolopyridinyl groups.

[0045] Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinolinyl, isoquinolinyl, pyridopyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl, and pteridinyl groups. Particular heteroaryl groups are those derived from thiophenyl, pyrrolyl, benzothiophenyl, benzofuranyl, indolyl, pyridinyl, quinolinyl, imidazolyl, oxazolyl and pyrazinyl.

[0046] Examples of representative heteroaryls include the following:

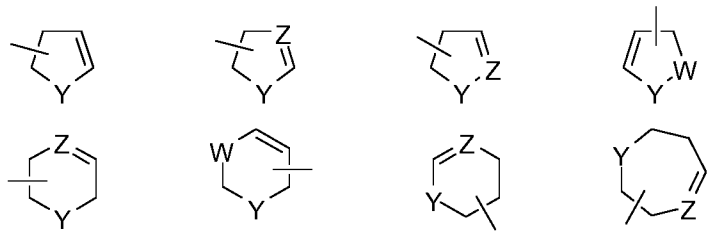


wherein each Y is selected from >C=O, NH, O and S.

[0047] 'Heterocycloalkyl' means a non-aromatic fully saturated ring structure, monocyclic, fused polycyclic, spirocyclic, or bridged polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. The heterocycloalkyl ring structure may have from 4 to 12 ring members, in particular from 4 to 10 ring members and more particularly from 4 to 7 ring members. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heterocycloalkyl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. Examples of heterocyclic rings include, but are not limited to azetidinyl, oxetanyl, thietanyl, pyrrolidinyl (*e.g.* 1-pyrrolidinyl, 2-

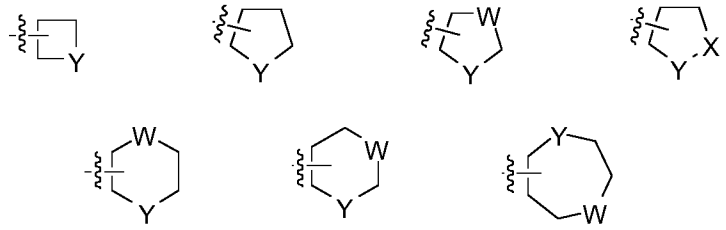
pyrrolidinyl and 3-pyrrolidinyl), tetrahydrofuranyl (*e.g.* 1-tetrahydrofuranyl, 2-tetrahydrofuranyl and 3-tetrahydrofuranyl), tetrahydrothiophenyl (*e.g.* 1-tetrahydrothiophenyl, 2-tetrahydrothiophenyl and 3-tetrahydrothiophenyl), piperidinyl (*e.g.* 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), tetrahydropyranyl (*e.g.* 4-tetrahydropyranyl), tetrahydrothiopyranyl (*e.g.* 4-tetrahydrothiopyranyl), morpholinyl, thiomorpholinyl, dioxanyl, or piperazinyl.

[0048] As used herein, the term 'heterocycloalkenyl' means a 'heterocycloalkyl', which comprises at least one double bond. Particular examples of heterocycloalkenyl groups are shown in the following illustrative examples:



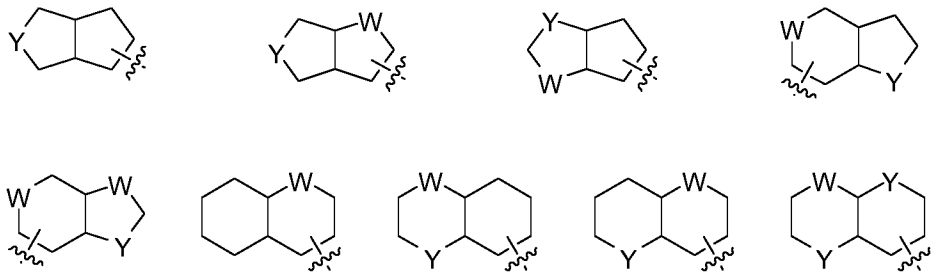
wherein each W is selected from CH_2, NH, O and S; each Y is selected from NH, O, C(=O), SO_2, and S; and each Z is selected from N or CH.

[0049] Particular examples of monocyclic rings are shown in the following illustrative examples:



wherein each W and Y is independently selected from -CH_2-, -NH-, -O- and –S-.

[0050] Particular examples of fused bicyclic rings are shown in the following illustrative examples:

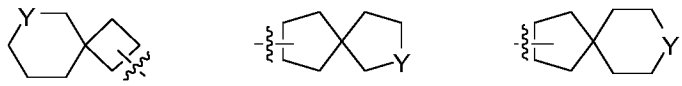


wherein each W and Y is independently selected from -CH_2-, -NH-, -O- and –S-.

[0051] Particular examples of bridged bicyclic rings are shown in the following illustrative examples:

wherein W is selected from -CH-, and -N-, and Y is selected from -CH_2-, -NH-, -O- and –S-.

[0052] Particular examples of spirocyclic rings are shown in the following illustrative examples:



wherein each Y is selected from -CH_2-, -NH-, -O- and –S-.

[0053] 'Hydroxyl' refers to the radical -OH.

[0054] 'Oxo' refers to the radical =O.

[0055] 'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

[0056] 'Sulfo' or 'sulfonic acid' refers to a radical such as $-SO_3H$.

[0057] 'Thiol' refers to the group -SH.

[0058] As used herein, term 'substituted with one or more' refers to one to four substituents. In one embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

[0059] 'Thioalkoxy' refers to the group –S-alkyl where the alkyl group has the number of carbon atoms specified. In particular the term refers to the group -S-C_{1-6} alkyl. Particular thioalkoxy groups are thiomethoxy, thioethoxy, n-thiopropoxy, isothiopropoxy, n-thiobutoxy, tert-thiobutoxy, sec-thiobutoxy, n-thiopentoxy, n-thiohexoxy, and 1,2-dimethylthiobutoxy. Particular thioalkoxy groups are lower thioalkoxy, i.e. with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

[0060] One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non-aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

[0061] 'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0062] 'Pharmaceutically acceptable salt' refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g. an

alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

[0063] 'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

[0064] 'Prodrugs' refers to compounds, including derivatives of the compounds of the invention,which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0065] 'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, EtOH, acetic acid and the like. The compounds of the invention may be prepared e.g. in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. 'Solvate' encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0066] 'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

[0067] 'Effective amount' means the amount of a compound of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The "effective amount" can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[0068] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (i.e. causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset.

[0069] The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0070] 'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e. arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically, (e.g. stabilization of a discernible symptom), physiologically, (e.g. stabilization of a physical parameter), or both. In a further embodiment, "treating" or "treatment" relates to slowing the progression of the disease.

[0071] As used herein the term 'allergic disease(s)' refers to the group of conditions characterized by a hypersensitivity disorder of the immune system including, allergic airway disease (e.g. asthma, rhinitis), sinusitis, eczema and hives, as well as food allergies or allergies to insect venom.

[0072] As used herein the term 'asthma' as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate the cause.

[0073] As used herein the term 'inflammatory disease(s)' refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, allergic airway disease (e.g. asthma, rhinitis), chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), endotoxin-driven disease states (e.g. complications after bypass surgery or chronic endotoxin states contributing to e.g. chronic cardiac failure), and related diseases involving cartilage, such as that of the joints. Particularly the term refers to rheumatoid arthritis, osteoarthritis, allergic airway disease (e.g. asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases. More particularly the term refers to rheumatoid arthritis, chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases

[0074] As used herein the term 'autoimmune disease(s)' refers to the group of diseases including obstructive airways disease, including conditions such as COPD, asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantile asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythrematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto's and autoimmune thyroiditis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, systemic lupus erythematosis, type I diabetes mellitus and inflammatory bowel disease.As used herein the term 'proliferative disease(s)' refers to conditions such as cancer (e.g. uterine leiomyosarcoma or prostate cancer), myeloproliferative disorders (e.g. polycythemia vera, essential thrombocytosis and myelofibrosis), leukemia (e.g. acute myeloid leukaemia, acute and chronic lymphoblastic leukemia), multiple myeloma, psoriasis, restenosis, scleroderma or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

[0075] As used herein, the term 'cancer' refers to a malignant or benign growth of cells in skin or in body organs, for example but without limitation, breast, prostate, lung, kidney, pancreas, stomach or bowel. A cancer tends to infiltrate into adjacent tissue and spread (metastasise) to distant organs, for example to bone, liver, lung or the brain. As used herein the term cancer includes both metastatic tumour cell types (such as but not limited to, melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, and mastocytoma) and types of tissue carcinoma (such as but not limited to, colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, renal cancer, gastric cancer, glioblastoma, primary liver cancer, ovarian cancer, prostate cancer and uterine leiomyosarcoma). In particular, the term 'cancer' refers to acute lymphoblastic leukemia, acute myeloidleukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T -Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, asopharyngeal cancer, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer,

Waldenstrom macroglobulinemia, and Wilms tumor. In another particular embodiment, the term cancer refers to pancreatic cancer, liver cancer, hepatocellular carcinoma (HCC), breast cancer, or colon cancer.

[0076] As used herein the term 'leukemia' refers to neoplastic diseases of the blood and blood forming organs. Such diseases can cause bone marrow and immune system dysfunction, which renders the host highly susceptible to infection and bleeding. In particular the term leukemia refers to acute myeloid leukaemia (AML), and acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukaemia (CLL). In another particular embodiment, the term leukemia refers to T-cell acute lymphoblastic leukemia (T-ALL), chronic lymphocytic leukemia (CLL), or diffuse large B-cell lymphoma (DLBCL).

[0077] As used herein the term 'transplantation rejection' refers to the acute or chronic rejection of cells, tissue or solid organ allo- or xenografts of e.g. pancreatic islets, stem cells, bone marrow, skin, muscle, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus, or graft-versus-host diseases.

[0078] As used herein the term 'diseases involving impairment of cartilage turnover' includes conditions such as osteoarthritis, psoriatic arthritis, juvenile rheumatoid arthritis, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, Tietze syndrome or costal chondritis, fibromyalgia, osteochondritis, neurogenic or neuropathic arthritis, arthropathy, endemic forms of arthritis like osteoarthritis deformans endemica, Mseleni disease and Handigodu disease; degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma and ankylosing spondylitis.

[0079] As used herein the term 'congenital cartilage malformation(s)' includes conditions such as hereditary chondrolysis, chondrodysplasias and pseudochondrodysplasias, in particular, but without limitation, microtia, anotia, metaphyseal chondrodysplasia, and related disorders.

[0080] As used herein the term 'disease(s) associated with hypersecretion of IL6' includes conditions such as Castleman's disease, multiple myeloma, psoriasis, Kaposi's sarcoma and/or mesangial proliferative glomerulonephritis.

[0081] As used herein the term 'disease(s) associated with hypersecretion of interferons includes conditions such as systemic and cutaneous lupus erythematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, psoriasis, rheumatoid arthritis.

[0082] 'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, and the solvates of the pharmaceutically acceptable salts where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

[0083] When ranges are referred to herein, for example but without limitation, C_{1-8} alkyl, the citation of a range should be considered a representation of each member of said range.

[0084] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgaard, 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a

suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particular such prodrugs are the C_{1-8} alkyl, C_{2-8} alkenyl, C_{6-10} optionally substituted aryl, and (C_{6-10} aryl)-(C_{1-4} alkyl) esters of the compounds of the invention.

[0085] As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitro (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as 11C, 18F, 15O and 13N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0086] All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

[0087] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

[0088] Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e. as (+) or (-) isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

[0089] 'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

[0090] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0091] The compounds of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

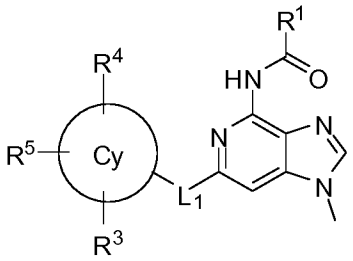
[0092] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0093] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

THE INVENTION

[0094] The present invention is based on the identification of novel compounds, and their ability to act as inhibitors of JAKs and that they may be useful for the treatment of prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons. In particular, the compounds of the invention may show selectivity towards JAK1 and TYK2. In another particular embodiment, the compounds of the invention may show low potency against JAK2. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for prophylaxis and/or treatment of allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons by administering the compounds of the invention.

[0095] Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula (I):



I

wherein

R^1 is

– C_{3-4} cycloalkyl, optionally substituted with one or more independently selected C_{1-4} alkyl, halo, or -CN,

– $-CH_3$, $-CH_2-OH$, $-CH_2-CN$, $-CH_2-CH_2-CN$, or

– $-OCH_3$;

L_1 is $-NR^2-$; or -O-;

Cy is

– phenyl, or

– 6 membered heteroaryl comprising 1, 2 or 3 nitrogen heteroatoms;

R^2 is

– H,

– C_{1-4} alkyl optionally substituted with one or more OH,

– C_{2-4} alkenyl comprising one double bond;

R^3 is

– H,

– halo,

– C_{1-4} alkyl optionally substituted with one or more halo, or

– C_{1-4} alkoxy optionally substituted with one or more halo;

R^4 is H, or halo or C_{1-4} alkyl;

R^5 is halo, -CN, or $–L_2-R^6$, wherein

L_2 is

– a bond,

– -W-, or

– $-C_{1-2}$ alkylene-W-;

W is -S-, -O-, $-NR^7-$, -C(=O)-, -C(=O)O-, $-C(=O)NR^7-$, $-NR^7C(=O)-$, $-SO_2-$, $-SO_2NR^7-$, or $-NR^7SO_2-$;

R^6 is

– H,

– C_{1-6} alkyl optionally substituted with one or more independently selected R^8 groups,

– C_{3-7} cycloalkyl, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– C_{6-10} aryl optionally substituted with one or more groups independently selected from R^9, or

– 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9;

or when is R^5 is $–L_2-R^6$, R^5 and R^2, together may form a fused 6 membered heterocycloalkyl ring with Cy;R^7 is H, or C_{1-4} alkyl;

R^8 is

– -OH,

– -CN,

– halo, or

– C_{1-4} alkoxy; and

each R^9 is independently selected from

– oxo,

– halo,

– -CN,

– C_{1-4} alkyl, and

– $-SO_2-C_{1-4}$ alkyl, which alkyl is optionally substituted with one or more halo.

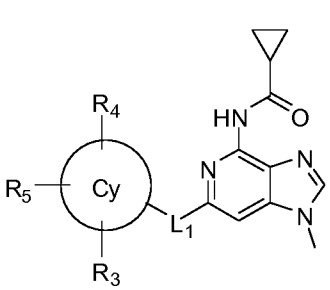
[0096] In one embodiment, the compound of the invention is according to Formula I, wherein R^1 is $-OCH_3$.

[0097] In one embodiment, the compound of the invention is according to Formula I, wherein R^1 is $-CH_3$.

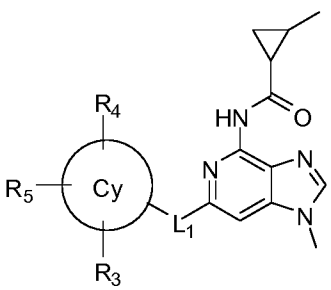
[0098] In one embodiment, the compound of the invention is according to Formula I, wherein R^1 is C_{3-4} cycloalkyl. In a particular embodiment, R^1 is cyclopropyl, or cyclobutyl. In a more particular embodiment, R^1 is cyclopropyl.

[0099] In one embodiment, the compound of the invention is according to Formula I, wherein R^1 is C_{3-4} cycloalkyl substituted with one or more independently selected C_{1-4} alkyl, halo, or –CN. In a particular embodiment, R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one or more independently selected C_{1-4} alkyl, halo, or –CN. In another particular embodiment, R^1 is C_{3-4} cycloalkyl substituted with one or more independently selected $–CH_3$, F, or –CN. In yet another particular embodiment, R^1 is is cyclopropyl, or cyclobutyl, each of which substituted with one or more independently selected $–CH_3$, F, or –CN. In a more particular embodiment, R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one or two independently selected C_{1-4} alkyl, halo, or –CN. In another more particular embodiment, R^1 is C_{3-4} cycloalkyl substituted with one or two independently selected $–CH_3$, F, or –CN. In yet another more particular embodiment, R^1 is is cyclopropyl, or cyclobutyl, each of which substituted with one or two independently selected $–CH_3$, F, or –CN. In a most particular embodiment, R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one C_{1-4} alkyl, halo, or –CN. In another more particular embodiment, R^1 is C_{3-4} cycloalkyl substituted with one $–CH_3$, F, or –CN. In yet another most particular embodiment, R^1 is is cyclopropyl, or cyclobutyl, each of which substituted with one $–CH_3$, F, or –CN.

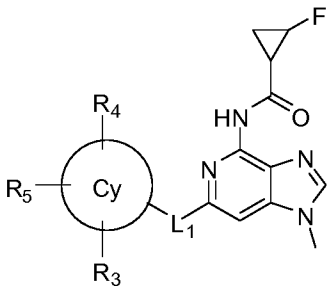
[0100] In one embodiment, the compound of the invention is according to Formula IIa, IIb, or IIc:



IIa,



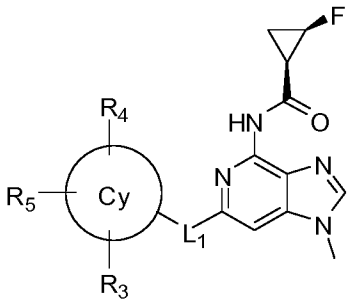
IIb, or



IIc

wherein L_1, Cy, R^3, R^4, and R^5 are as described above.

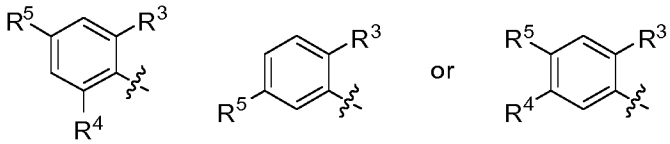
[0101] In one embodiment, the compound of the invention is according to Formula III:



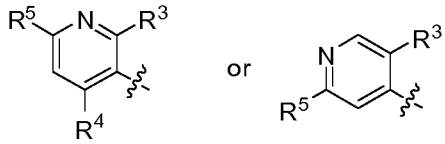
III

wherein L_1, Cy, R^3, R^4, and R^5 are as described above.

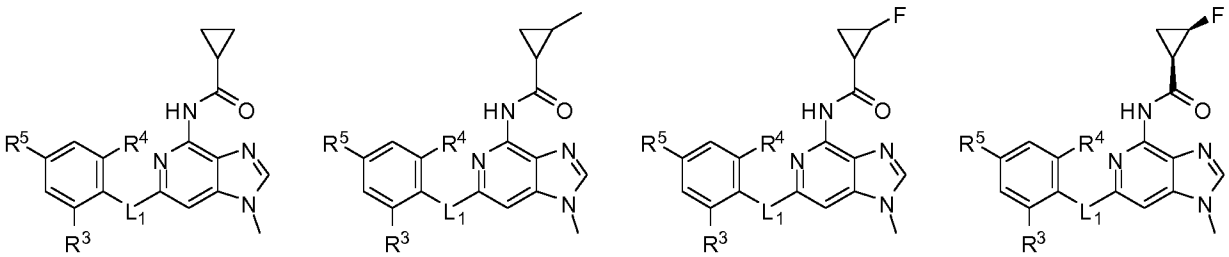
[0102] In one embodiment, the compound of the invention is according to any one of Formula I-III, wherein Cy is phenyl. In a particular embodiment, Cy is:



[0103] In another embodiment, the compound of the invention is according to any one of Formula I-III, wherein Cy is 6 membered heteroaryl comprising 1, 2, or 3 nitrogen heteroatoms. In a particular embodiment, Cy is pyridinyl. In a particular embodiment, Cy is:



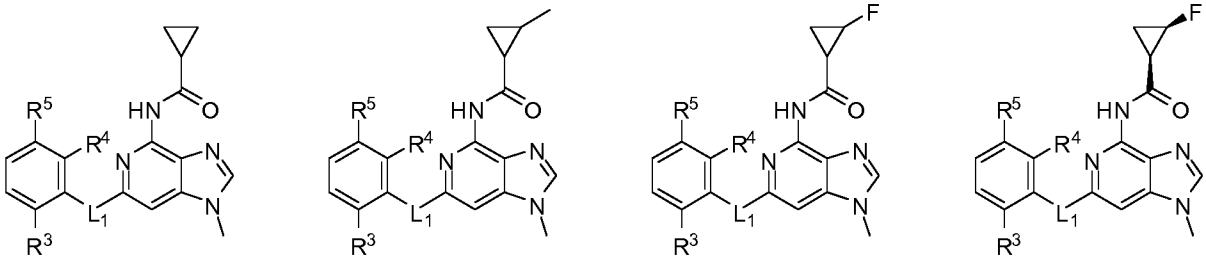
[0104] In one embodiment, the compound of the invention is according to Formula IVa, IVb, IVc, or IVd:



IVa, IVb, IVc, or IVd

wherein L_1, R^3, R^4 and R^5 are as defined above.

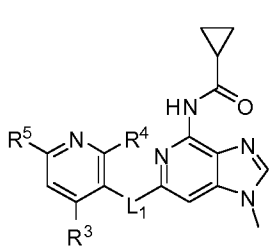
[0105] In one embodiment, the compound of the invention is according to Formula IVe, IVf, IVg, or IVh



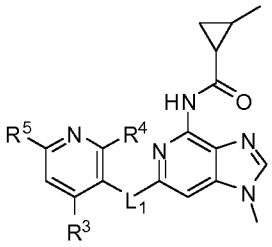
IVe, IVf, IVg, or IVh

wherein L_1, R^3, R^4 and R^5 are as defined above.

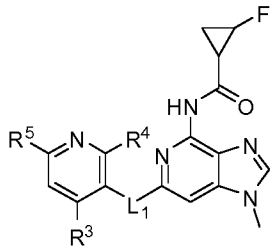
[0106] In one embodiment, the compound of the invention is according to Formula IVi, IVj, IVk, or IVl



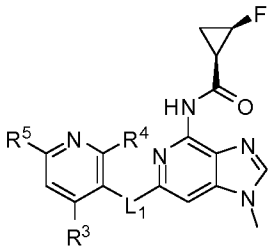
IVi,



IVj,



IVk, or



IVl

wherein L_1, R^3, R^4 and R^5 are as defined above.

[0107] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is H.

[0108] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is halo. In a particular embodiment, R^3 is F, or Cl. In a more particular embodiment, R^3 is F.

[0109] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is C_{1-4} alkyl. In a particular embodiment, R^3 is $-CH_3$, or $-CH_2CH_3$.

[0110] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is C_{1-4} alkyl substituted with one or more halo. In a particular embodiment, R^3 is $-CH_3$, or $-CH_2CH_3$, each of which is substituted with one or more halo. In another particular embodiment, R^3 is C_{1-4} alkyl substituted with one or more F. In a more particular embodiment, R^3 is $-CH_3$, or $-CH_2CH_3$, each of which is substituted with one or more F. In a most particular embodiment, R^3 is $-CF_3$, $-CHF_2$, $-CH_2CHF_2$, or $-CH_2CF_3$. In yet a most particular embodiment, R^3 is $-CH_2CHF_2$.

[0111] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is C_{1-4} alkoxy. In a particular embodiment, R^3 is $-OCH_3$, or $-OCH_2CH_3$.

[0112] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^3 is C_{1-4} alkoxy substituted with one or more halo. In a particular embodiment, R^3 is $-OCH_3$, or $-OCH_2CH_3$, each of which is substituted with one or more halo. In another particular embodiment, R^3 is C_{1-4} alkoxy substituted with one or more F. In a more particular embodiment, R^3 is $-OCH_3$, or $-CH_2CH_3$, each of which is substituted with one or more F. In a most particular embodiment, R^3 is $-OCF_3$, or $-OCHF_2$.

[0113] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^4 is H.

[0114] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^4 is halo or C_{1-4} alkyl. In a particular embodiment, R^4 is F, Cl, $-CH_3$, or $-CH_2CH_3$.

[0115] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is halo, or –CN. In a particular embodiment, R^5 is F, Cl, or –CN. In a more particular embodiment, R^5 is –CN.

[0116] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, R^6 is as defined above and L_2 is a bond.

[0117] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, R^6 is as defined above, L_2 is a W, and W is -S-, -O-, $-NR^7-$, -C(=O)-, -C(=O)-, $-C(=O)NR^7-$, $-NR^7C(=O)-$, $-SO_2-$, $-SO_2NR^7-$, or $-NR^7SO_2-$. . In a particular embodiment, W is $-NR^7-$, $-C(=O)NR^7-$, $-NR^7C(=O)-$, or $-NR^7SO_2-$. In another particular embodiment, W is -O-, or $-SO_2-$. In a more particular embodiment, W is $-C(=O)NR^7-$. In a most particular embodiment, W is $-SO_2-$.

[0118] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, R^6 is as defined above, L_2 is a $-C_{1-2}$ alkylene-W-, and –W- is as defined above. In a particular, embodiment, L_2 is a $-CH_2$-W-, or $-CH(CH_3)$-W-, and –W- is as defined above. In a more particular embodiment, W is $-NR^7-$, $-C(=O)NR^7-$, $-NR^7C(=O)-$, or $-NR^7SO_2-$. In another more particular embodiment, W is -O-, or $-SO_2-$. In a most particular embodiment, L_2 is $-CH_2-NR^7C(=O)-$, or $-CH_2-NR^7SO_2-$.

[0119] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^7 is H, or C_{1-4} alkyl. In a particular embodiment, R^7 is H, or CH_3.

[0120] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is H

[0121] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is C_{1-6} alkyl. In a particular embodiment, R^6 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$. In a most particular embodiment, R^6 is $-CH_3$.

[0122] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is C_{1-6} alkyl substituted with one or more independently selected R^8 groups. In a another embodiment, R^6 is $-CH_3$, $-CH_2CH_3$ or $-CH_2CH_2CH_3$, each of which is substituted with one or more independently selected R^8 groups. In a particular embodiment, R^6 is C_{1-6} alkyl substituted with one, two or three independently selected R^8 groups. In another particular embodiment, R^6 is $-CH_3$, $-CH_2CH_3$ or $-CH_2CH_2CH_3$, each of which is substituted with one, two or three independently selected R^8 groups. In a more particular embodiment, R^6 is C_{1-6} alkyl substituted with one R^8 group. In another more particular embodiment, R^6 is $-CH_3$, $-CH_2CH_3$ or $-CH_2CH_2CH_3$, each of which is substituted with one R^8 group.

[0123] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is C_{3-7} cycloalkyl. In a particular embodiment, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0124] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is C_{3-7} cycloalkyl, substituted with one or more groups independently selected from R^9. In another embodiment, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one or more groups independently selected from R^9. In a particular embodiment, R^6 is C_{3-7} cycloalkyl, substituted with one or two groups independently selected from R^9. In another particular embodiment, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one or two groups independently selected from R^9. In a more particular embodiment, R^6 is C_{3-7} cycloalkyl, substituted with one R^9. In another more

particular embodiment, R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one R^9.

[0125] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S. In a particular embodiment, R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl.

[0126] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or more groups independently selected from R^9. In another embodiment, R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is substituted with one or more groups independently selected from R^9. In a particular embodiment, R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or two groups independently selected from R^9. In another particular embodiment, R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is substituted with one or two groups independently selected from R^9. In a more particular embodiment, R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one R^9. In another more particular embodiment, R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is substituted with one R^9. In a most particular embodiment, R^6 is azetidinyl substituted with one R^9.

[0127] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S. In a particular embodiment, R^6 is dihydropyranyl.

[0128] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or more groups independently selected from R^9. In another embodiment, R^6 is tetrahydropyridinyl, substituted with one or more groups independently selected from R^9. In a particular embodiment, R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one or two groups independently selected from R^9. In another particular embodiment, R^6 is tetrahydropyridinyl, substituted with one or two groups independently selected from R^9. In a more particular embodiment, R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one R^9. In another more particular embodiment, R^6 is tetrahydropyridinyl, substituted with one R^9.

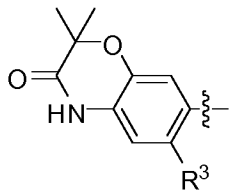
[0129] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is C_{6-10} aryl. In a particular embodiment, R^6 is phenyl.

[0130] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is R^6, and R^6 is C_{6-10} aryl, substituted with one or more groups independently selected from R^9. In another embodiment, R^6 is phenyl, substituted with one or more groups independently selected from R^9. In a particular embodiment, R^6 is C_{6-10} aryl, substituted with one or two groups independently selected from R^9. In another particular embodiment, R^6 is phenyl substituted with one or two groups independently selected from R^9. In a more particular embodiment, R^6 is C_{6-10} aryl, substituted with one R^9. In another more particular embodiment, R^6 is phenyl substituted with one R^9.

[0131] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S. In a particular embodiment, R^6 is pyrazolyl, imidazolyl, or pyridinyl.

[0132] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^5 is $-L_2-R^6$, L_2 is as defined above and R^6 is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, substituted with one or more groups independently selected from R^9. In another embodiment, R^6 is pyrazolyl, imidazolyl, or pyridinyl, each of which is substituted with one or more groups independently selected from R^9. In a particular embodiment, R^6 is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, substituted with one or two groups independently selected from R^9. In another particular embodiment, R^6 is pyrazolyl, imidazolyl, or pyridinyl, each of which is substituted with one or two groups independently selected from R^9. In a more particular embodiment, R^6 is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, substituted with one R^9. In another more particular embodiment, R^6 is pyrazolyl, imidazolyl, or pyridinyl, each of which is substituted with one R^9. In a most particular embodiment, R^6 is pyrazolyl substituted with one R^9.

[0133] In one embodiment, R^5 is $-L_2-R^6$, R^5 and R^2, together may form a fused 6 membered heterocycloalkyl ring with Cy. In a particular embodiment, R^5, R^2 and Cy together are:



wherein is as described above.

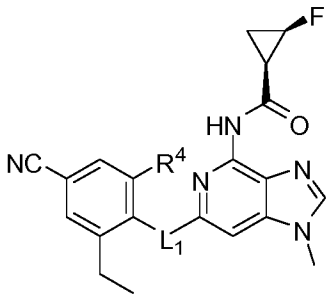
[0134] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^8 is –OH, -CN, halo, or C_{1-4} alkoxy. In a particular embodiment, R^8 is –OH, -CN, F, Cl, or $-OCH_3$, $-OCH_2CH_3$. In a more particular embodiment, R^8 is –OH, -CN, or F.

[0135] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^9 is oxo.

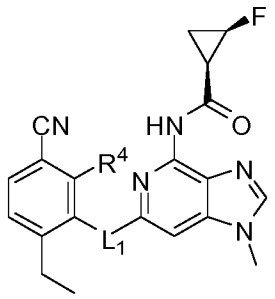
[0136] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^9 is halo, -CN, or C_{1-4} alkyl. In a particular embodiment, R^9 is -CN, F, Cl, or $-CH_3$, $-CH_2CH_3$. In a more particular embodiment, R^9 is -CN, F, or $-CH_3$.

[0137] In one embodiment, the compound of the invention is according to any one of Formula I-IVl, wherein R^9 is $-SO_2-C_{1-4}$ alkyl, which alkyl is optionally substituted with one or more halo. In a particular, R^9 is $-SO_2CH_3$, or $-SO_2CH_2CH_3$. In another particular, R^9 is $-SO_2CH_3$, or $-SO_2CH_2CH_3$, each of which is substituted with one or more halo. In more particular embodiment, R^9 is $-SO_2CHF_2$.

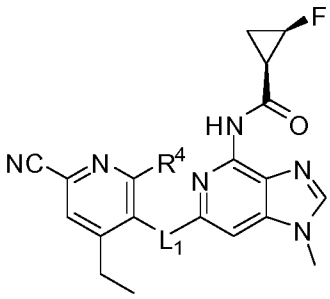
[0138] In one embodiment, the compound of the invention in according to any one of Formula Va-Ve



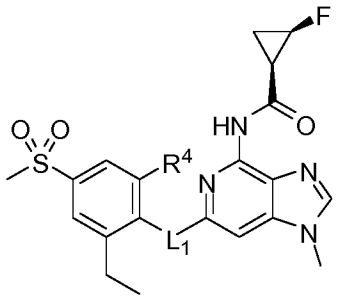
Va,



Vb,

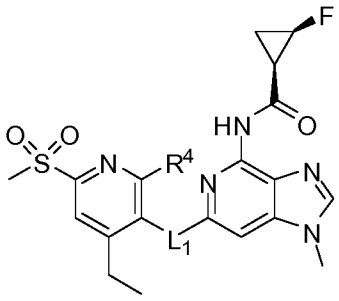


Vc



Vd,

or



Ve

Wherein L_1 and R^4 are as described above.

[0139] In one embodiment, the compound of the invention in according to any one of Formula Va-Ve, wherein R^4 is H.

[0140] In one embodiment, the compound of the invention is according to any one of Formula Va-Ve, wherein R^4 is halo or C_{1-4} alkyl. In a particular embodiment, R^4 is F, or $-CH_3$.

[0141] In one embodiment, the compound of the invention is according to any one of Formula I-Vc, wherein L_1 is –O-.

[0142] In one embodiment, the compound of the invention is according to any one of Formula I-Vc, wherein L_1 is $-NR^2-$. In a particular embodiment, R^2 is H.

[0143] In one embodiment, the compound of the invention is according to any one of Formula I-Vc wherein L_1 is $-NR^2-$, wherein R^2 is C_{1-4} alkyl. In a particular embodiment, R^2 is $-CH_3$, or $-CH_2CH_3$.

[0144] In one embodiment, the compound of the invention is according to any one of Formula I-Vc, wherein L_1 is $-NR^2-$, wherein R^2 is C_{1-4} alkyl substituted with one or more OH. In a particular embodiment, R^2 is $-CH_2CH_3$, or $-CH_2CH_2CH_3$, each of which is substituted with one or more OH. In a more particular embodiment, R^2 is $-CH_2CH(OH)CH_2OH$.

[0145] In one embodiment, the compound of the invention is according to any one of Formula I-Vc, wherein L_1 is $-NR^2-$, wherein R^2 is C_{2-4} alkenyl comprising on double bond. In a particular embodiment, R^2 is $-CH_2-CH=CH_2$.

[0146] In one embodiment, the compound of the invention is selected from:

N-[6-(4-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-5-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-5-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-5-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c] pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-5-fluoro-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[[4-ethyl-6-(1-methylsulfonylazetidin-3-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c] pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[[6-[1-(difluoromethylsulfonyl)azetidin-3-yl]-4-ethyl-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[[4-ethyl-6-(methanesulfonamidomethyl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c] pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[[4-ethyl-6-[[methyl(methylsulfonyl)amino]methyl]-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide,

N-[6-(4-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide,

N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[2-ethyl-4-(methanesulfonamidomethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide,

N-[6-[2-ethyl-6-fluoro-N-methyl-4-[[methyl(methylsulfonyl)amino]methyl]anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide,

N-[6-[4-[[difluoromethylsulfonyl(methyl)amino]methyl]-2-ethyl-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(2-chloro-4-cyano-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-(1-methyl-6-phenoxy-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide,

N-[6-(4-cyano-2-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-(2-ethyl-4,6-difluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(2-ethyl-4,6-difluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(2-ethyl-4-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[4-cyano-2-(2,2-difluoroethyl)-6-fluoro-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide,

N-[6-(2-ethyl-4-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[4-cyano-2-(2,2-difluoroethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[4-cyano-2-(2,2-difluoroethyl)-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide,

N-[6-[4-cyano-2-(2,2-difluoroethyl)-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide,

N-[6-[4-cyano-2-(difluoromethoxy)-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide,

N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

(2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-[2-ethyl-N-methyl-4-(2-thienyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropane carboxamide,

N-[6-[2-ethyl-N-methyl-4-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

(1R,2R)-N-[6-[2-ethyl-N-methyl-4-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-3,3-difluoro-cyclobutanecarboxamide,

N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-3,3-difluoro-cyclobutanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-hydroxy-acetamide,

(1S,2S)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

1-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(5-cyano-2-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(5-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(5-cyano-N,2-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(5-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-methyl-cyclopropanecarboxamide,

(1S)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2,2-dimethyl-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-1-methyl-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2,2-difluoro-cyclopropanecarboxamide,

2-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl] acetamide,

3-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]propanamide,

4-ethyl-5-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]pyridine-2-carboxamide,

3-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-methyl-benzamide,

4-ethyl-3-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

methyl N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl] carbamate,

(1R,2R)-N-[6-[(4-ethyl-6-methylsulfonyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

(1R,2R)-N-[6-(2-ethyl-5-methoxy-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-1-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[4-cyano-2-(difluoromethoxy)-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c] pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-5-fluoro-benzamide,

(1R,2R)-N-[6-(2-ethyl-4-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(5-ethyl-2-methoxy-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(2-cyano-5-ethyl-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[[6-(dimethylamino)-4-ethyl-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(2-cyano-5-ethyl-3-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(5-ethyl-2-methyl-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(3-ethyl-2-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-N,2-diethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-ethyl-4-[ethyl-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-5-fluoro-benzamide,

(1R,2R)-N-[6-[allyl-(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-(2,3-dihydroxypropyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-(2-ethyl-6-fluoro-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

(1R,2R)-N-[6-(2-ethyl-6-fluoro-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(4-ethyl-6-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-benzamide,

3-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

(1R,2R)-N-[6-(2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(2-ethyl-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(5-chloro-4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(2-chloro-6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-(difluoromethoxy)-5-fluoro-benzamide,

3-(difluoromethoxy)-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-methyl-benzamide,

(1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-[(2R)-2-hydroxypropyl]benzamide,

N-(cyanomethyl)-3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-methyl-benzamide,

(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[[4-ethyl-6-(1-methylpyrazol-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[2-ethyl-6-fluoro-N-methyl-4-(1-methylpyrazol-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[N,2-dimethyl-4-(1-methylpyrazol-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-chloro-2,2-dimethyl-3-oxo-4H-1,4-benzoxazin-7-yl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-2-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-N,2-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-ethyl-5-fluoro-4-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-benzamide,

(1R,2R)-N-[6-(2-chloro-4-cyano-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-chloro-4-[[7-chloro-4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-5-fluoro-benzamide,

(1R,2R)-N-[6-(4-cyano-2-ethyl-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

3-ethyl-4-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-benzamide,

(1R,2R)-N-[6-(2-chloro-4-cyano-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-chloro-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-2-fluoro-N-[6-[(6-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

(1R,2R)-N-[6-[5-(cyanomethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(3-ethyl-5-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[4-cyano-5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

2-(difluoromethoxy)-5-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

(1R,2R)-N-[6-[(6-cyano-4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-(6-(4-cyano-2-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide,

methyl N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate,

(1R,2R)-N-[6-[2-ethyl-6-fluoro-N-methyl-4-(1-methylsulfonylethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-(cyanomethyl)-3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-[6-[(5-ethyl-1-methyl-2-oxo-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide, and

Methyl-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] carbamate.

[0147] In aparticualr embodiment, the compound of the invention is selected from:

N-[6-[[4-ethyl-6-(1-methylsulfonylazetidin-3-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[[4-ethyl-6-(methanesulfonamidomethyl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide,

(1S,2S)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(2-cyano-5-ethyl-3-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-benzamide,

3-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide,

4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-(difluoromethoxy)-5-fluoro-benzamide,

(1R,2R)-N-[6-[[4-ethyl-6-(1-methylpyrazol-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[2-ethyl-6-fluoro-N-methyl-4-(1-methylpyrazol-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

(1R,2R)-N-[6-(4-chloro-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide,

N-(6-(4-cyano-2-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide, and

(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide.

[0148] In one embodiment a compound of the invention is not an isotopic variant.

[0149] In one aspect a compound of the invention according to any one of the embodiments herein described is present as the free base.

[0150] In one aspect a compound of the invention according to any one of the embodiments herein described is a pharmaceutically acceptable salt.

[0151] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of the compound.

[0152] In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of a pharmaceutically acceptable salt of a compound.

[0153] While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

[0154] While specified groups for each embodiment have generally been listed above separately, a compound of the invention may be one for which one or more variables (for example, R groups) is selected from one or more embodiments according to any of the Formula(e) listed above. Therefore, the present invention is intended to include all combinations of variables from any of the disclosed embodiments within its scope.

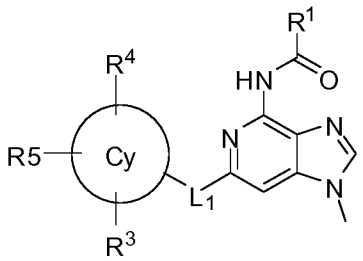
[0155] Alternatively, the exclusion of one or more of the specified variables from a group or an embodiment, or combinations thereof is also contemplated by the present invention.

[0156] In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

[0157] Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgard, H, 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly useful are the C_1 to C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds of the invention.

CLAUSES

1. A compound according to Formula I:



I

wherein

R^1 is

– $C_{3\text{-}4}$ cycloalkyl, optionally substituted with one or more independently selected $C_{1\text{-}4}$ alkyl, halo, or -CN,

– $-CH_3$, $-CH_2$-OH, $-CH_2$-CN, $-CH_2$-CH_2-CN, or

– $-OCH_3$;

L_1 is $-NR^2$-; or -O-;

Cy is

– phenyl, or

– 6 membered heteroaryl comprising 1, 2, or 3 nitrogen heteroatoms;

R^2 is

– H,

– C_{1-4} alkyl optionally substituted with one or more OH,

– C_{2-4} alkenyl comprising one double bond;

R^3 is

– H,

– halo,

– C_{1-4} alkyl optionally substituted with one or more halo, or

– C_{1-4} alkoxy optionally substituted with one or more halo;

R^4 is H, or halo or C_{1-4} alkyl;

R^5 is halo, -CN, or $–L_2-R^6$, wherein

L_2 is

– a bond,

– -W-, or

– -C_{1-2} alkylene-W-;

W is -S-, -O-, -NR^7-, -C(=O)-, -C(=O)O-, -C(=O)NR^7-, -NR^7C(=O)-, -SO_2-, -SO_2NR^7-, or -NR^7SO_2-;

R^6 is

– H,

– C_{1-6} alkyl optionally substituted with one or more independently selected R^8 groups,

– C_{3-7} cycloalkyl, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– C_{6-10} aryl optionally substituted with one or more groups independently selected from R^9, or

– 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9;

or when is R^5 is $–L_2-R^6$, R^5 and R^2, together may form a fused 6 membered heterocycloalkyl ring with Cy;

R^7 is H, or C_{1-4} alkyl;

R^8 is

– -OH,

– -CN,

– halo, or

– C_{1-4} alkoxy; and

each R^9 is independently selected from

– oxo,

– halo,

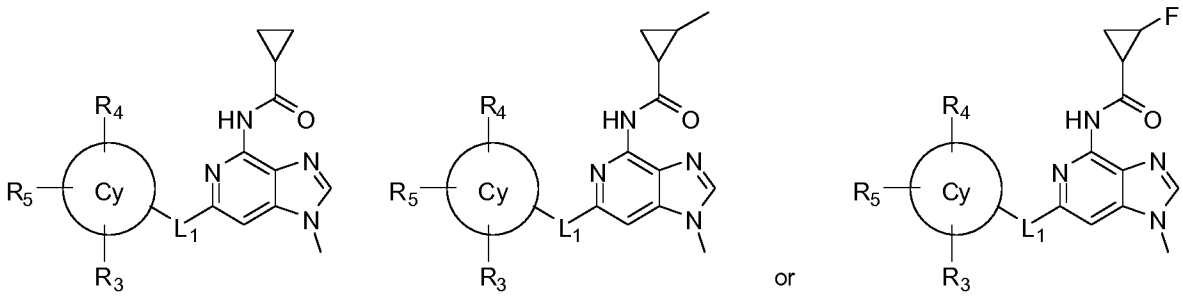
– -CN,

– C_{1-4} alkyl, and

– -SO_2-C_{1-4} alkyl, which alkyl is optionally substituted with one or more halo; or

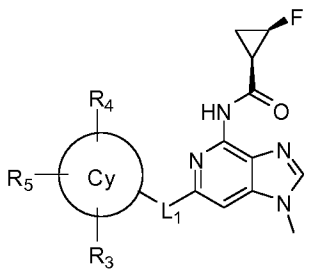
a pharmaceutically acceptable salt, or a solvate, or the salt of a pharmaceutically acceptable salt thereof.

2. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is -OCH_3, or -CH_3.
3. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is cyclopropyl.
4. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is C_{3-4} cycloalkyl substituted with one, or two independently selected C_{1-4} alkyl, halo, or –CN.
5. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one or two independently selected C_{1-4} alkyl, halo, or –CN.
6. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one or two independently selected –CH_3, F, or –CN.
7. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one or two independently selected –CH_3, or F.
8. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein R^1 is R^1 is cyclopropyl, or cyclobutyl, each of which is substituted with one –CH_3, F, or –CN.
9. A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to Formula IIa, IIb, or IIc:



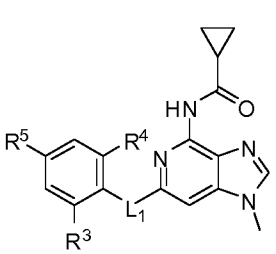
IIa, IIb, or IIc

10. A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to Formula III:

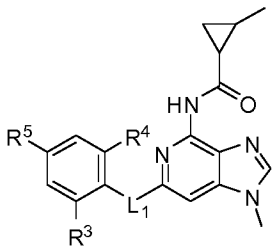


III

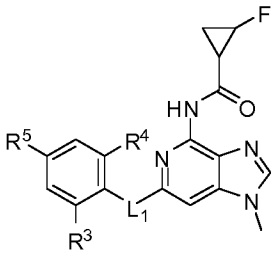
11. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-10, wherein Cy is phenyl.
12. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-10, wherein Cy is pyridinyl.
13. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein the compound is according to Formula IVa, IVb, IVc, or IVd:



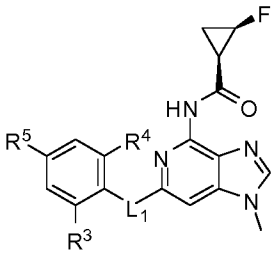
IVa,



IVb,

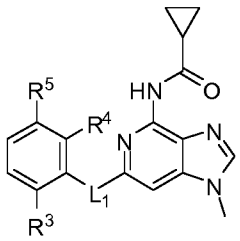


IVc, or

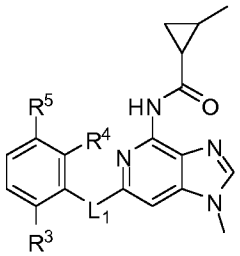


IVd

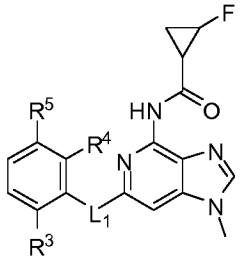
14. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein the compound is according to Formula IVe, IVf, IVg, or IVh:



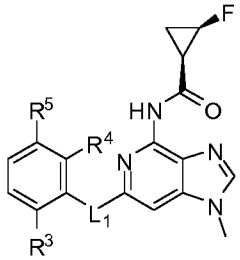
IVe,



IVf,

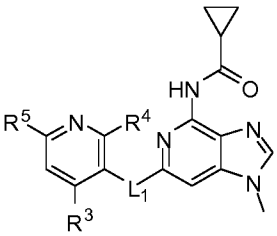


IVg, or

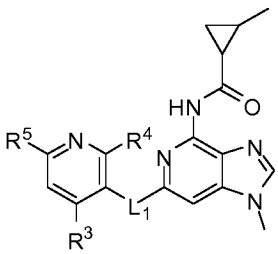


IVh

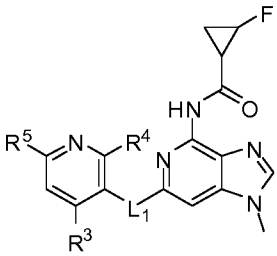
15. A compound or pharmaceutically acceptable salt thereof according to clause 1, wherein the compound is according to Formula IVi, IVj, IVk, or IVl:



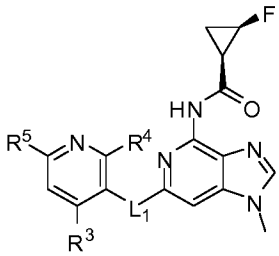
IVi,



IVj,



IVk, or



IVl

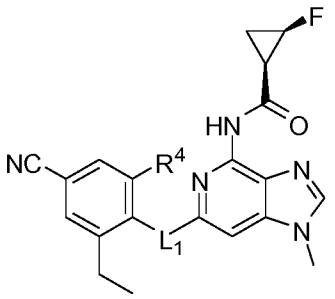
16. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is H.
17. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is halo.
18. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is F.
19. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is C_{1-4} alkyl.

20. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is $-CH_3$, or $-CH_2CH_3$.
21. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is C_{1-4} alkyl substituted with one or more halo.
22. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is $-CH_2CHF_2$.
23. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is C_{1-4} alkoxy.
24. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is $-OCH_3$, or $-OCH_2CH_3$.
25. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is C_{1-4} alkoxy substituted with one or more halo.
26. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-15, wherein R^3 is $-OCF_3$, or $-OCHF_2$.
27. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-26, wherein R^4 is H.
28. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-26, wherein R^4 is halo or C_{1-4} alkyl.
29. A compound or pharmaceutically acceptable salt thereof according to clause 28, wherein R^4 is F, Cl, $-CH_3$, or $-CH_2CH_3$.
30. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-29, wherein R^5 is halo.
31. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-29, wherein R^5 is –CN.
32. A compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-29, wherein R^5 is $–L_2-R^6$.
33. A compound or pharmaceutically acceptable salt thereof according to clause 32, wherein L_2 is a bond.
34. A compound or pharmaceutically acceptable salt thereof according to clause 32, wherein L_2 is W, and W is $-NR^7-$, $-C(=O)NR^7-$, $-NR^7C(=O)-$, or $-NR^7SO_2-$.
35. A compound or pharmaceutically acceptable salt thereof according to clause 32, wherein L_2 is $-C_{1-2}$ alkylene-W-.
36. A compound or pharmaceutically acceptable salt thereof according to clause 35, wherein L_2 is $-CH_2-W-$, or $-CH(CH_3)-W-$.
37. A compound or pharmaceutically acceptable salt thereof according to clause 35 or 36, wherein W is $-NR^7-$, $-C(=O)NR^7-$, $-NR^7C(=O)-$, or $-NR^7SO_2-$.
38. A compound or pharmaceutically acceptable salt thereof according to clause 35 or 36, wherein W is -O-, or $-SO_2-$.

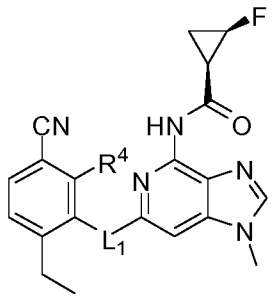
39. A compound or pharmaceutically acceptable salt thereof according to clause 32, wherein L_2 is $-CH_2-NR^7C(=O)-$, or $-CH_2-NR^7SO_2-$.
40. A compound or pharmaceutically acceptable salt thereof according to clause 34, 37, or 39, wherein R^7 is H, or CH_3.
41. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is H.
42. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is C_{1-6} alkyl.
43. A compound or pharmaceutically acceptable salt thereof, according to clause 42, wherein R^6 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$.
44. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is C_{1-6} alkyl substituted with one, two or three independently selected R^8 groups.
45. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is $-CH_3$, $-CH_2CH_3$ or $-CH_2CH_2CH_3$, each of which is substituted with one, two or three independently selected R^8 groups.
46. A compound or pharmaceutically acceptable salt thereof, according to clause 44 or 45, wherein R^8 is –OH, -CN, halo, or C_{1-4} alkoxy.
47. A compound or pharmaceutically acceptable salt thereof, according to clause 44 or 45, wherein R^8 is –OH, -CN, F, Cl, or $-OCH_3$, $-OCH_2CH_3$.
48. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is C_{3-7} cycloalkyl.
49. A compound or pharmaceutically acceptable salt thereof, according to clause 42, wherein R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.
50. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is C_{3-7} cycloalkyl substituted with one, two or three independently selected R^9 groups.
51. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is substituted with one, two or three independently selected R^9 groups.
52. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S.
53. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl.
54. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one, two or three independently selected R^9 groups.

55. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is azetidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is substituted with one, two or three independently selected R^9 groups.
56. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S.
57. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is dihydropyranyl.
58. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, substituted with one, two or three independently selected R^9 groups.
59. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is tetrahydropyridinyl substituted with one, two or three independently selected R^9 groups.
60. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is is C_{6-10} aryl.
61. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is phenyl.
62. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is C_{6-10} aryl, substituted with one, two or three independently selected R^9 groups.
63. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is phenyl substituted with one, two or three independently selected R^9 groups.
64. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S.
65. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is pyrazolyl, imidazolyl, or pyridinyl.
66. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, substituted with one, two or three independently selected R^9 groups.
67. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 32-40, wherein R^6 is pyrazolyl, imidazolyl, or pyridinyl, each of which is substituted with one, two or three independently selected R^9 groups.
68. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 50, 51, 54, 55, 58, 59, 62, 63, 66, or 67, wherein R^9 is oxo.
69. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 50, 51, 54, 55, 58, 59, 62, 63, 66, or 67, wherein R^9 is halo, -CN, or C_{1-4} alkyl.

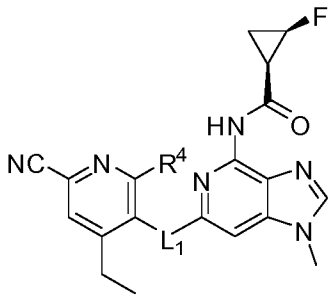
70. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 50, 51, 54, 55, 58, 59, 62, 63, 66, or 67, wherein R^9 is -CN, F, Cl, or $-CH_3$, $-CH_2CH_3$.
71. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 50, 51, 54, 55, 58, 59, 62, 63, 66, or 67, wherein R^9 is $-SO_2-C_{1-4}$ alkyl, which alkyl is optionally substituted with one or more halo.
72. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 50, 51, 54, 55, 58, 59, 62, 63, 66, or 67, wherein R^9 is $-SO_2CHF_2$.
73. A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to any one of Formula Va-Ve:



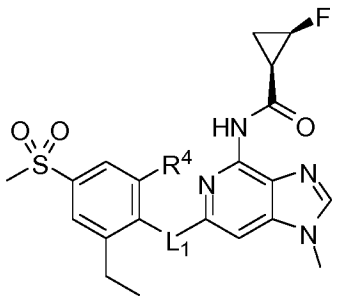
Va,



Vb,

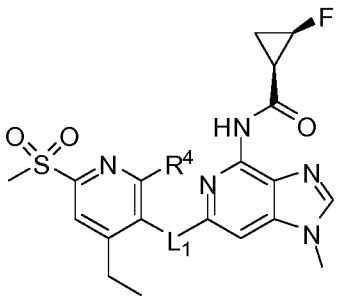


Vc



Vd,

or



Ve

74. A compound or pharmaceutically acceptable salt thereof, according to clause 73, wherein R^4 is H.
75. A compound or pharmaceutically acceptable salt thereof, according to clause 73, wherein R^4 is F, or $-CH_3$.
76. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-75, wherein L_1 is –O-.
77. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-75, wherein L_1 is $-NR^2-$.
78. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is H.
79. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is C_{1-4} alkyl.
80. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is $-CH_3$, or $-CH_2CH_3$.
81. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is C_{1-4} alkyl substituted with one or more OH..

82. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is $-CH_2CH(OH)CH_2OH$.
83. A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^2 is $-CH_2-CH=CH_2$.
84. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-83.
85. A pharmaceutical composition, according to clause 84, comprising a further therapeutic agent.
86. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-83, or a pharmaceutical composition according to clause 84 or 85, for use in medicine.
87. A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-83, or a pharmaceutical composition according to clause 84 or 85, for use in the prophylaxis and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.
88. The use of a compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-83, or a pharmaceutical composition according to clause 84 or 85, in medicine.
89. The use of a compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-83, or a pharmaceutical composition according to clause 84 or 85, in the prophylaxis and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.
90. A method of prophylaxis and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons, comprising administering an amount of a compound or pharmaceutically acceptable salt thereof according to any one of clauses 1-83, or a pharmaceutical composition according to clause 84 or 85, sufficient to effect said treatment, or prophylaxis.
91. The pharmaceutical composition according to clause 85, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.
92. The compound for use according to clause 86, or the use according to clause 89, or the method according to clause 90, wherein the inflammatory condition is rheumatoid arthritis.
93. The compound for use according to clause 86, or the use according to clause 89, or the method according to clause 90, wherein the inflammatory condition is IBD.

94. The compound for use according to clause 86, or the use according to clause 89, or the method according to clause 90, wherein the autoimmune disease is psoriasis.
95. The compound for use according to clause 86, or the use according to clause 89, or the method according to clause 90, wherein the proliferative condition is cancer.
96. The compound for use according to clause 86, or the use according to clause 89, or the method according to clause 90, wherein the proliferative condition is selected from myelofibrosis, T-cell acute lymphoblastic leukemia (T-ALL), multiple myeloma, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), pancreatic cancer, liver cancer, hepatocellular carninoma (HCC), lung cancer, breast cancer, and colon cancer.

PHARMACEUTICAL COMPOSITIONS

[0158] When employed as a pharmaceutical, a compound of the invention is typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound of the invention according to Formula I. Generally, a compound of the invention is administered in a pharmaceutically effective amount. The amount of compound of the invention actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound of the invention administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0159] The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, a compound of the invention is preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

[0160] The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term 'unit dosage forms' refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound of the invention according to Formula I is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0161] Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compound of the inventions of a similar nature:

a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint or orange flavoring.

[0162] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound of the invention according to Formula I in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[0163] Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as an ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

[0164] A compound of the invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

[0165] The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

[0166] A compound of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

[0167] The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

[0168] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active compound of the invention according to Formula I per tablet) in a tablet press.

Formulation 2 - Capsules

[0169] A compound of the invention according to Formula I may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active compound of the invention according to Formula I per capsule).

Formulation 3 - Liquid

[0170] A compound of the invention according to Formula I (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient water may then be added with stirring. Further sufficient water may be then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

[0171] A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 450-900 mg tablets (150-300 mg of active compound of the invention according to Formula I) in a tablet press.

Formulation 5 - Injection

[0172] A compound of the invention according to Formula I may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

[0173] Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of A compound of the invention according to Formula I (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

METHODS OF TREATMENT

[0174] A compound of the invention may be used as a therapeutic agent for the treatment of conditions in mammals that are causally related or attributable to aberrant activity of JAK. In particular, conditions related to aberrant activity of JAK1 and/or TYK2. Accordingly, the compounds and pharmaceutical compositions of the invention find use as therapeutics for preventing and/or treating allergic diseases, inflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or hypersecretion of interferons in mammals including humans.

[0175] In one aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use as a medicament.

[0176] In another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament.

[0177] In yet another aspect, the present invention provides a method of treating a mammal having, or at risk of having a disease disclosed herein, said method comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a particular aspect, the present invention provides a method of treating a mammal having, or at risk of having allergic diseases, inflammatory diseases, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or hypersecretion of interferons.

[0178] In a method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with an allergic reaction, said method comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention as herein described. In a specific embodiment, the allergic reaction is selected from allergic airway disease, sinusitis, eczema and hives, food allergies and allergies to insect venom.

[0179] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of an allergic reaction. In a specific embodiment, the allergic reaction is selected from allergic airway disease, sinusitis, eczema and hives, food allergies and allergies to insect venom.

[0180] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, or prophylaxis of an allergic reaction. In a specific embodiment, the allergic reaction is selected from allergic airway disease, sinusitis, eczema and hives, food allergies and allergies to insect venom.

[0181] In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with an inflammatory condition. The methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention as herein described. In a specific embodiment, the inflammatory condition is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma) and inflammatory bowel diseases.

[0182] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of an inflammatory condition. In a specific embodiment, the inflammatory condition is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma) and inflammatory bowel diseases.

[0183] In yet another aspect, the present invention provides the compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of an inflammatory condition. In a specific embodiment, the inflammatory condition is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma) and inflammatory bowel diseases.

[0184] In additional method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with an autoimmune disease. The methods comprise administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, psoriasis, type I diabetes mellitus and inflammatory bowel disease. In a more particular embodiment, the autoimmune disease is psoriasis.

[0185] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of an autoimmune disease. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, psoriasis, type I diabetes mellitus and inflammatory bowel disease. In a more particular embodiment, the autoimmune disease is psoriasis.

[0186] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of an autoimmune disease. In a specific embodiment, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, psoriasis, type I diabetes mellitus and inflammatory bowel disease. In a more particular embodiment, the autoimmune disease is psoriasis.

[0187] In further method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with a proliferative disease, said methods comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the proliferative disease is selected from cancer (*e.g.* solid tumors such as uterine leiomyosarcoma or prostate cancer), leukemia (*e.g.* AML, ALL or CLL), multiple myeloma and psoriasis. In a more specific embodiment, the proliferative disease is selected from myelofibrosis, T-cell acute lymphoblastic leukemia (T-ALL), multiple myeloma, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), pancreatic cancer, liver cancer, hepatocellular carninoma (HCC), lung cancer, breast cancer, and colon cancer.

[0188] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of a proliferative disease. In a specific embodiment, the proliferative disease is selected from cancer (*e.g.* solid tumors such as uterine leiomyosarcoma or prostate cancer), leukemia (*e.g.* AML, ALL or CLL), multiple myeloma and psoriasis. In a more specific embodiment, the proliferative disease is selected from myelofibrosis, T-cell acute lymphoblastic leukemia (T-ALL), multiple myeloma, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL),

pancreatic cancer, liver cancer, hepatocellular carninoma (HCC), lung cancer, breast cancer, and colon cancer.

[0189] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of a proliferative disease. In a specific embodiment, the proliferative disease is selected from cancer (*e.g.* solid tumors such as uterine leiomyosarcoma or prostate cancer), leukemia (*e.g.* AML, ALL or CLL), multiple myeloma and psoriasis. In a more specific embodiment, the proliferative disease is selected from myelofibrosis, T-cell acute lymphoblastic leukemia (T-ALL), multiple myeloma, chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), pancreatic cancer, liver cancer, hepatocellular carninoma (HCC), lung cancer, breast cancer, and colon cancer.

[0190] In further method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with transplantation rejection, said methods comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the transplantation rejection is organ transplant rejection.

[0191] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of transplantation rejection. In a specific embodiment, the transplantation rejection is organ transplant rejection.

[0192] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment and/or prophylaxis of of transplantation rejection. In a specific embodiment, the transplantation rejection is organ transplant rejection.

[0193] In a method of treatment aspect, this invention provides a method of treatment, and/or prophylaxis in a mammal susceptible to or afflicted with diseases involving impairment of cartilage turnover, which method comprises administering a therapeutically effective amount of a compound of the invention, or one or more of the pharmaceutical compositions herein described.

[0194] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of diseases involving impairment of cartilage turnover.

[0195] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of diseases involving impairment of cartilage turnover.

[0196] The present invention also provides a method of treatment and/or prophylaxis of congenital cartilage malformations, which method comprises administering an effective amount of one or more of the pharmaceutical compositions or compounds of the invention herein described.

[0197] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of congenital cartilage malformations.

[0198] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of congenital cartilage malformations.

[0199] In further method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with diseases associated with hypersecretion of IL6, said methods comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the disease associated with hypersecretion of IL6 is selected from Castleman's disease and mesangial proliferative glomerulonephritis.

[0200] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of diseases associated with hypersecretion of IL6. In a specific embodiment, the disease associated with hypersecretion of IL6 is selected from Castleman's disease and mesangial proliferative glomerulonephritis.

[0201] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of diseases associated with hypersecretion of IL6. In a specific embodiment, the disease associated with hypersecretion of IL6 is selected from Castleman's disease and mesangial proliferative glomerulonephritis.

[0202] In further method of treatment aspects, this invention provides methods of treatment and/or prophylaxis of a mammal susceptible to or afflicted with diseases associated with hypersecretion of interferons, said methods comprising administering an effective condition-treating or condition-preventing amount of one or more of the pharmaceutical compositions or compounds of the invention herein described. In a specific embodiment, the disease associated with hypersecretion of interferons is selected from systemic and cutaneous lupus erythematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, psoriasis, and rheumatoid arthritis.

[0203] In another aspect the present invention provides a compound of the invention for use in the treatment, and/or prophylaxis of diseases associated with hypersecretion of interferons. In a specific embodiment, the disease associated with hypersecretion of interferons is selected from systemic and cutaneous lupus erythematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, psoriasis, and rheumatoid arthritis.

[0204] In yet another aspect, the present invention provides a compound of the invention, or a pharmaceutical composition comprising a compound of the invention for use in the manufacture of a medicament for the treatment, and/or prophylaxis of diseases associated with hypersecretion of interferons. In a specific embodiment, the disease associated with hypersecretion of interferons is selected from systemic and cutaneous lupus erythematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, psoriasis, and rheumatoid arthritis.

[0205] As a further aspect of the invention there is provided a compound of the invention for use as a pharmaceutical especially in the treatment and/or prophylaxis of the aforementioned conditions and

diseases. Also provided herein is the use of the present compounds in the manufacture of a medicament for the treatment and/or prophylaxis of one of the aforementioned conditions and diseases.

[0206] A particular regimen of the present method comprises the administration to a subject suffering from a disease involving inflammation, of an effective amount of a compound of the invention for a period of time sufficient to reduce the level of inflammation in the subject, and preferably terminate the processes responsible for said inflammation. A special embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject patient suffering from or susceptible to the development of rheumatoid arthritis, for a period of time sufficient to reduce or prevent, respectively, inflammation in the joints of said patient, and preferably terminate, the processes responsible for said inflammation.

[0207] A further particular regimen of the present method comprises the administration to a subject suffering from a disease condition characterized by cartilage or joint degradation (*e.g.* rheumatoid arthritis and/or osteoarthritis) of an effective amount of a compound of the invention for a period of time sufficient to reduce and preferably terminate the self-perpetuating processes responsible for said degradation. A particular embodiment of the method comprises administering of an effective amount of a compound of the invention to a subject patient suffering from or susceptible to the development of osteoarthritis, for a period of time sufficient to reduce or prevent, respectively, cartilage degradation in the joints of said patient, and preferably terminate, the self-perpetuating processes responsible for said degradation. In a particular embodiment said compound may exhibit cartilage anabolic and/or anti-catabolic properties.

[0208] Injection dose levels range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 2 g/day for a 40 to 80 kg human patient.

[0209] For the prophylaxis and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to five and especially two to four and typically three oral doses per day are representative regimens. Using these dosing patterns, each dose provides from about 0.01 to about 20 mg/kg of a compound of the invention, with particular doses each providing from about 0.1 to about 10 mg/kg and especially about 1 to about 5 mg/kg.

[0210] Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

[0211] When used to prevent the onset of a condition, a compound of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

[0212] A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compounds that demonstrate

the same or a similar therapeutic activity and that are determined to safe and efficacious for such combined administration. In a specific embodiment, co-administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

[0213] In one embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention is administered as a medicament. In a specific embodiment, said pharmaceutical composition additionally comprises a further active ingredient.

[0214] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of a disease involving inflammation; particular agents include, but are not limited to, immunoregulatory agents *e.g.* azathioprine, corticosteroids (*e.g.* prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, Mycophenolate Mofetil, muromonab-CD3 (OKT3, *e.g.* Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

[0215] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of arthritis (*e.g.* rheumatoid arthritis); particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, auranofin, sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, and ciclosporin), and biological DMARDS (for example but without limitation Infliximab, Etanercept, Adalimumab, Rituximab, and Abatacept).

[0216] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of proliferative disorders; particular agents include but are not limited to: methotrexate, leukovorin, adriamycin, prenisone, bleomycin, cyclophosphamide, 5-fluorouracil, paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, tamoxifen, toremifene, megestrol acetate, anastrozole, goserelin, anti-HER^2 monoclonal antibody (*e.g.* HerceptinTM), capecitabine, raloxifene hydrochloride, EGFR inhibitors (*e.g.* Iressa®, Tarceva™, Erbitux™), VEGF inhibitors (*e.g.* Avastin™), proteasome inhibitors (*e.g.* Velcade™), Glivec® and hsp90 inhibitors (*e.g.* 17-AAG). Additionally, a compound of the invention may be administered in combination with other therapies including, but not limited to, radiotherapy or surgery. In a specific embodiment the proliferative disorder is selected from cancer, myeloproliferative disease and leukaemia.

[0217] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of autoimmune diseases, particular agents include but are not limited to: glucocorticoids, cytostatic agents (*e.g.* purine analogs), alkylating agents, (e.g nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds, and others), antimetabolites (*e.g.* methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (*e.g.* dactinomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies (*e.g.* anti-CD20, anti-CD25 or anti-CD3 (OTK3) monoclonal antibodies, Atgam® and Thymoglobuline®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (*e.g.* IFN-β), TNF binding proteins (*e.g.* infliximab (Remicade™), etanercept (Enbrel™), or adalimumab (Humira™)), mycophenolate, Fingolimod and Myriocin.

[0218] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of transplantation rejection, particular agents include but are not limited to: calcineurin inhibitors (*e.g.* cyclosporin or tacrolimus (FK506)), mTOR inhibitors (*e.g.* sirolimus, everolimus), anti-proliferatives (*e.g.* azathioprine, mycophenolic acid), corticosteroids (*e.g.* prednisolone, hydrocortisone), Antibodies (*e.g.* monoclonal anti-IL-2Rα receptor antibodies, basiliximab, daclizumab), polyclonal anti-T-cell antibodies (*e.g.* anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG)).

[0219] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of asthma and/or rhinitis and/or COPD, particular agents include but are not limited to: beta2-adrenoceptor agonists (*e.g.* salbutamol, levalbuterol, terbutaline and bitolterol), epinephrine (inhaled or tablets), anticholinergics (*e.g.* ipratropium bromide), glucocorticoids (oral or inhaled) Long-acting β2-agonists (*e.g.* salmeterol, formoterol, bambuterol, and sustained-release oral albuterol), combinations of inhaled steroids and long-acting bronchodilators (*e.g.* fluticasone/salmeterol, budesonide/formoterol), leukotriene antagonists and synthesis inhibitors (*e.g.* montelukast, zafirlukast and zileuton), inhibitors of mediator release (*e.g.* cromoglycate and ketotifen), biological regulators of IgE response (*e.g.* omalizumab), antihistamines (*e.g.* ceterizine, cinnarizine, fexofenadine) and vasoconstrictors (*e.g.* oxymethazoline, xylomethazoline, nafazoline and tramazoline).

[0220] Additionally, a compound of the invention may be administered in combination with emergency therapies for asthma and/or COPD, such therapies include oxygen or heliox administration, nebulized salbutamol or terbutaline (optionally combined with an anticholinergic (*e.g.* ipratropium), systemic steroids (oral or intravenous, *e.g.* prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone), intravenous salbutamol, non-specific beta-agonists, injected or inhaled (*e.g.* epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, *e.g.* glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bamiphylline), inhalation anesthetics that have a bronchodilatory effect (*e.g.* isoflurane, halothane, enflurane), ketamine and intravenous magnesium sulfate.

[0221] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of inflammatory bowel disease (IBD), particular agents include but are not limited to: glucocorticoids (*e.g.* prednisone, budesonide) synthetic disease modifying, immunomodulatory agents (*e.g.* methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and ciclosporin) and biological disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

[0222] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of SLE, particular agents include but are not limited to: Disease-modifying antirheumatic drugs (DMARDs) such as antimalarials (*e.g.* plaquenil, hydroxychloroquine), immunosuppressants (*e.g.* methotrexate and azathioprine), cyclophosphamide and mycophenolic acid; immunosuppressive drugs and analgesics, such as nonsteroidal anti-inflammatory

drugs, opiates (*e.g.* dextropropoxyphene and co-codamol), opioids (*e.g.* hydrocodone, oxycodone, MS Contin, or methadone) and the fentanyl duragesic transdermal patch.

[0223] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of psoriasis, particular agents include but are not limited to: topical treatments such as bath solutions, moisturizers, medicated creams and ointments containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort™), fluocinonide, vitamin D3 analogues (for example, calcipotriol), Argan oiland retinoids (etretinate, acitretin, tazarotene), systemic treatments such as methotrexate, cyclosporine, retinoids, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, fumaric acid esters or biologics such as Amevive™, Enbrel™, Humira™, Remicade™, Raptiva™ and ustekinumab (a IL-12 and IL-23 blocker). Additionally, a compound of the invention may be administered in combination with other therapies including, but not limited to phototherapy, or photochemotherapy (*e.g.* psoralen and ultraviolet A phototherapy (PUVA)).

[0224] In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of allergic reaction, particular agents include but are not limited to: antihistamines (e.g. cetirizine, diphenhydramine, fexofenadine, levocetirizine), glucocorticoids (e.g. prednisone, betamethasone, beclomethasone, dexamethasone), epinephrine, theophylline or anti-leukotrienes (e.g. montelukast or zafirlukast), anti-cholinergics and decongestants.

[0225] By co-administration is included any means of delivering two or more therapeutic agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation this is not essential. The agents may be administered in different formulations and at different times.

CHEMICAL SYNTHETIC PROCEDURES

General

[0226] The compound of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where 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. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

[0227] Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art (Greene, T W; Wuts, P G M;, 1991).

[0228] The following methods are presented with details as to the preparation of a compound of the invention as defined hereinabove and the comparative examples. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

[0229] All reagents were of commercial grade and were used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Column chromatography was performed on silica gel 60 (35-70 μm). Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). ^{1}H NMR spectra were recorded on a Bruker DPX 400 NMR spectrometer (400 MHz or a Bruker Advance 300 NMR spectrometer (300 MHz). Chemical shifts (δ) for 1H NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or the appropriate residual solvent peak, i.e. $CHCl_3$ (δ 7.27), as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quin), multiplet (m) and broad (br). Electrospray MS spectra were obtained on a Waters platform LC/MS spectrometer or with Waters Acquity H-Class UPLC coupled to a Waters Mass detector 3100 spectrometer. Columns used: Waters Acquity UPLC BEH C18 1.7μm, 2.1mm ID x 50mm L, Waters Acquity UPLC BEH C18 1.7 μm, 2.1mm ID x 30 mm L, or Waters Xterra MS 5μm C18, 100 x 4.6mm. The methods are using either MeCN/H_2O gradients (H_2O contains either 0.1% TFA or 0.1% NH_3) or MeOH /H_2O gradients (H_2O contains 0.05% TFA). Microwave heating was performed with a Biotage Initiator.

Table I. List of abbreviations used in the experimental section:

Abbréviation	**Definition**
μL	microliter
AcOH	Acetic acid
ALL	acute lymphoblastic leukemia
AML	acute myeloid leukaemia
APMA	4-aminophenylmercuric acetate
app t	Apparent triplet
Aq	aqueous
AUC	Area Under the Curve
Bd	Broad doublet
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	tert-Butyloxy-carbonyl
br s	broad singlet
BSA	Bovine serum albumine
Bt	Broad triplet
Cat.	Catalytic amount
CLL	chronic lymphoblastic leukaemia
COPD	chronic obstructive pulmonary disease
CV	Column volume
D	doublet
DCM	Dichloromethane
Desc'd	Described in details
DIPE	Diisopropylether
DIPEA	N,N-diisopropylethylamine

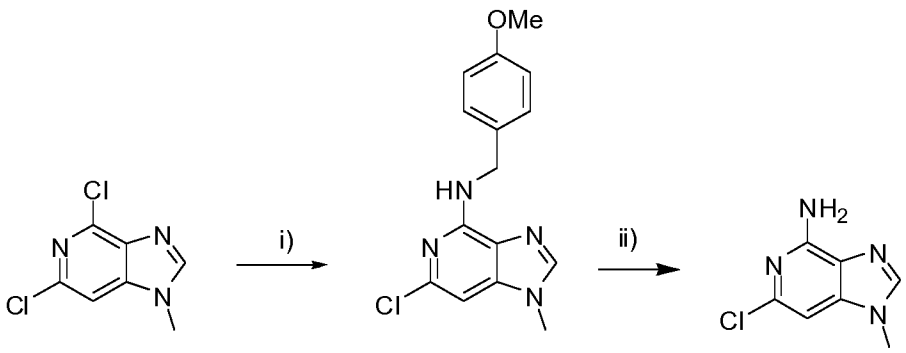
Abbréviation	Definition
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMB	Dimethoxybenzyl
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid
eq.	Equivalent
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FBS	Fetal bovine serum
FITC	Fluorescein Isothiocyanate
G	gram
GIST	gastrointestinal stromal tumor
H	hour
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
HRP	horseradish peroxydase
Int	Intermediate
IPF	idiopathic pulmonary fibrosis
kg	kilogram
L	liter
LC-MS	Liquid Chromatography- Mass Spectrometry
M	multiplet
MeCN	Acetonitrile
MeOH	Methanol
Mg	milligram
Min	minute
mL	millilitre
Mmol	millimoles
MMP	Matrix Metallo Proteinase
MS Ms'd	Mass measured by LC-MS
MW	Molecular weight
N.A.	Not available
NaH	Sodium hydride
NaHMDS	Sodium bis(trimethylsilyl)amide
NMR	Nuclear Magnetic Resonance
NSAID	non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
PBMC	Peripheral blood mononuclear cell
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on Carbon 10%

Abbréviation	Definition
$Pd_2(dba)_3$	Tris(dibenzylideneacetone) dipalladium(0)
$PdCl_2dppf$	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PMB	Para methoxy benzyl
ppm	part-per-million
q	quadruplet
QrtPCR	quantitative real-time PCR
QTL	quantitative trait loci
RPMI medium	Roswell Park Memorial Institute medium
s	singlet
sat	saturated

SYNTHETIC PREPARATION OF THE COMPOUNDS OF THE INVENTION

Example 1. General intermediates

1.1. Intermediates 1 and 2



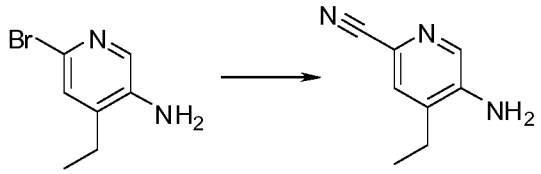
1.1.1. Step i): (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl) amine (intermediate 1)

[0230] 4,6-Dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (1 eq, 5.0 g) is dissolved in 4-para-methoxybenzylamine (2.24 eq, 8.3 mL) in a 20 mL sealed tube. The solution is heated to 110°C and is left stirring for 3 h. The reaction is diluted with water and extracted with DCM (3 x 100 mL). The combined organic layers are washed with 100 mL sat. brine, dried over Na_2SO_4 and concentrated *in vacuo*. Trituration of the obtained residue in MeOH yields the desired product.

1.1.2. Step ii): intermediate 2

[0231] A mixture of the product from step i) in TFA is stirred at room temperature for 1 h. The mixture is concentrated. The residue is purified preparative HPLC

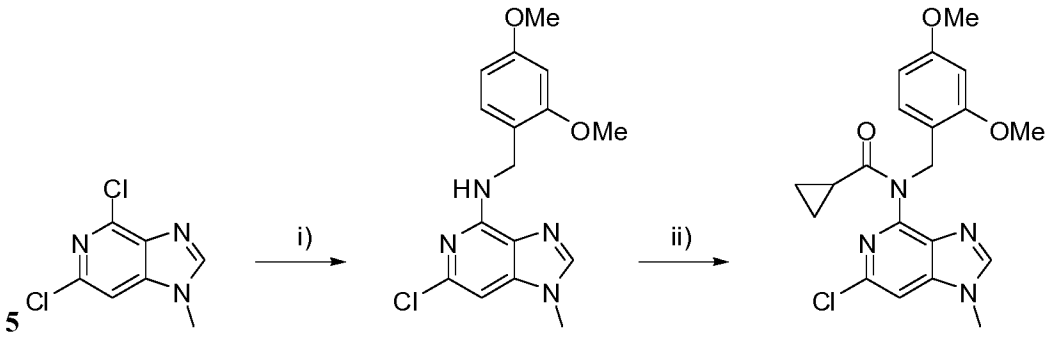
1.2. Intermediate 3



[0232] The entire reaction is performed under argon atmosphere. A solution of 6-bromo-4-ethylpyridin-3-ylamine (1 g, 4.976 mmol, 1.0 eq) and Zinc cyanide (0.44 g, 3.730 mmol, 0.75 eq) in DMF (10 mL) and DMA (5 mL) is stirred at 90 °C. After 15 min, $Pd(PPh_3)_4$ (0.57 g, 0.497 mmol, 0.1 eq) is added and reaction mixture is stirred at that temp for 3 h. The resulting mixture is diluted with water (100 mL) and extraction with EtOAc (5 x 20 mL) followed. Crude material is purified by Biotage SP1 Snap Si 25; 25 mL/min using a gradient of MeOH in DCM: 0-7% in 20 CV. The appropriate fractions are combined and evaporated *in vacuo* to give the desired product.

[0233] LC-MS: [M+H]+=418.01

1.3. Intermediate 4 / Intermediate 5



1.3.1. Step i): (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amine (intermediate 4)

[0234] 4,6-Dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (1 eq, 5.0 g) is dissolved in 2,4-dimethoxybenzylamine (2.24 eq, 8.3 mL) in a 20 mL sealed tube. The solution is heated to 110°C and left stirring for 3 h. The reaction is diluted with water and extracted with DCM (3 x 100 mL). The combined organic layers are washed with sat. brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Trituration of the obtained residue in MeOH yields the desired product.

1.3.2. Step ii): Cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amide (intermediate5)

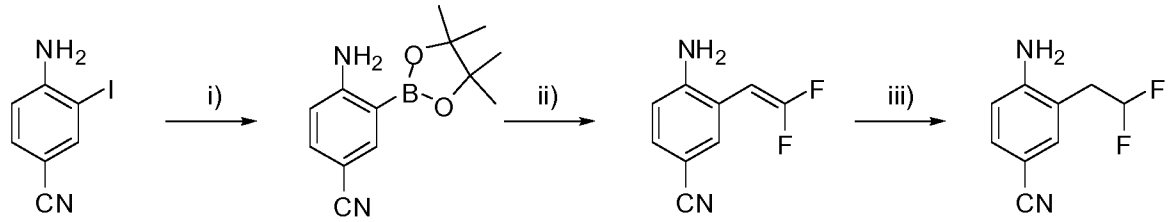
[0235] Intermediate 7 (1 eq, 500 mg) and and cyclopropanecarboxylic acid chloride (1.5 eq, 205 µL) are dissolved in anhydrous DCM (4 mL) in a sealed 10 mL tube. Dry pyridine (2 mL) is added and the reaction is heated to 45°C for 1 h. After completion of the reaction as shown by LC-MS, the reaction is diluted with water (25 mL) and DCM (50 mL). The organic layer is successively washed with sat. $NaHCO_3$ (25 mL) and sat. brine (25 mL). Drying over anhydrous sodium sulfate and concentration *in vacuo* yields the desired compound.

1.4. Intermediate 6

[0236] Toluene-4-sulfonic acid 2,2,2-trifluoroethyl ester (1 eq, 6.0 g) is dissolved in anhydrous THF (120 mL). The reaction is cooled down to -78°C, after which *n*-butyllithium (2.5M in hexane, 2.3 eq,

22 mL) is carefully added. The reaction is left stirring at this temperature for 2 h, after which the mixture is diluted with water and EtOAc. Extraction with EtOAc (3 x 100 mL) is performed. The combined organics are washed with sat. brine and dried over anhydrous Na_2SO_4. Purification of the crude through column chromatography (silica, petroleum ether/EtOAc; 95:5 to 80:20) yields the desired product.

1.5. Intermediate 7



1.5.1. Step i): 4-Amino-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzonitrile

[0237] $PdCl_2dppf$ (0.05 eq, 171 mg), potassium acetate (2 eq, 804 mg), bis(pinacolato)diboron (1.8 eq, 1.88 g) and 4-amino-3-iodobenzonitrile (1 eq, 1.0 g) are dissolved in anhydrous DMSO (10 mL) in a 20 mL microwave tube and the suspension is degassed under nitrogen atmosphere for 10 min. The reaction mixture is brought to 65°C and kept at this temperature under vigorous stirring overnight. After completion of the reaction as shown by LC-MS, the mixture is diluted with water and EtOAc. Extraction with EtOAc (3 x 50 mL) is performed. The combined organics are washed with sat. brine and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude is used as such in the following step.

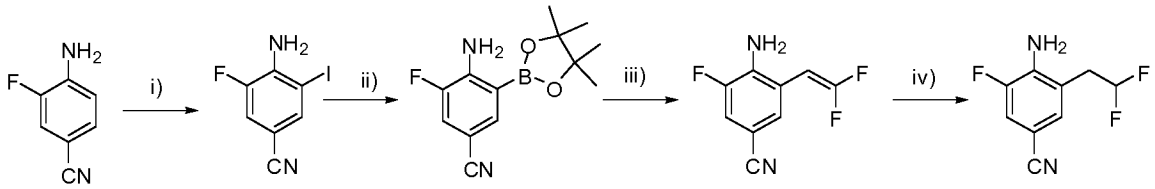
1.5.2. Step ii): 4-Amino-3-(2,2-difluorovinyl)benzonitrile

[0238] 4-Amino-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzonitrile (1 eq, 30.7 mmol) and toluene-4-sulfonic acid 2,2-difluorovinyl ester (1 eq, 7.2 g) are dissolved in a 4:1 solution of dioxane and water (175 mL). $Pd(dba)_3$ (0.05 eq, 1.4 g), HBF_4PCy_3 (0.1 eq, 1.1 g) and potassium phosphate (3 eq, 19.6 g) are added, after which the suspension is degassed under nitrogen atmosphere for 10 min and the reaction is brought to 60°C for 1 h. The suspension is then filtered over a Celite pad and concentrated *in vacuo*. The residue is dissolved in EtOAc and an aq. extraction with sat. $NaHCO_3$ and EtOAc (3 x 150 mL) is performed. The combined organics are washed with sat. brine, dried over Na_2SO_4 and concentrated. Purification of the crude through column chromatography (silica, petroleum ether/EtOAc; 95:5 to 90:10) yields the desired product.

1.5.3. Step iii): 4-Amino-3-(2,2-difluoroethyl)benzonitrile

[0239] A Parr reactor is charged with 4-amino-3-(2,2-difluorovinyl)benzonitrile (1 eq, 600 mg) in anhydrous MeOH (10 mL) at room temperature, while nitrogen gas is bubbled through the mixture. Pd/C(10 wt%, 0.05 eq, 160 mg) is added, the cylinder is sealed, filled with hydrogen gas (5 bar), and stirred at 50°C overnight. The resulting suspension is filtered over Celite pad, which is rinsed twice with MeOH. The filtrate is concentrated *in vacuo* and purified through silica chromatography (petroleum ether/DCM; 75:25 to 80:20) to yield the desired compound.

1.6. Intermediate 8



1.6.1. Step i): 2,4-Difluoro-6-iodoaniline

[0240] Iodine (1 eq, 19.7 g) is dissolved in EtOH (350 mL) at room temperature, and 2,4-difluoroaniline (1 eq, 8 mL) and silver sulfate (1 eq, 24.1 g) are added. The suspension is stirred at room temperature overnight. After completion of the reaction as seen by LC-MS, the silver salts are filtered off and the filtrate is concentrated *in vacuo*. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$ (3 x 100 mL). The organic layer is washed with sat. brine, dried over anhydrous sodium sulfate, and purified by column chromatography (silica, petroleum ether/EtOAc; 100:0 to 95:5) to give the desired product.

1.6.2. Step ii): 4-Amino-3-fluoro-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzonitrile

[0241] Bis(pinacolato)diboron (1.2 eq, 11.63 g) and potassium acetate (2 eq, 7.49 g) are added to a solution of 4-amino-3-fluoro-5-iodobenzonitrile (1 eq, 10.0 g) in anhydrous DMSO (50 mL). $PdCl_2dppf$ (0.05 eq, 1.56 g) is added and the suspension is degassed under a nitrogen atmosphere for 10 min. The reaction mixture is brought to 65°C and is kept at this temperature while stirring vigorously overnight. The mixture is then diluted with water and EtOAc and extraction with EtOAc (3 x 100 mL) is performed. The combined organics are washed with sat. brine and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude is used as such.

1.6.3. Step iii): 4-Amino-3-(2,2-difluorovinyl)-5-fluorobenzonitrile

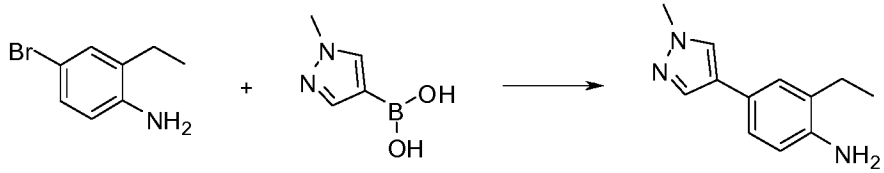
[0242] 4-Amino-3-fluoro-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)benzonitrile (1 eq, 38.2 mmol) and toluene-4-sulfonic acid 2,2-difluorovinyl ester (1 eq, 8.9 g) are dissolved in a 4:1 solution of dioxane and water (200 mL). $Pd_2(dba)_3$ (0.05 eq, 1.8 g), HBF_4PCy_3 (0.1 eq, 1.4 g) and potassium phosphate (3 eq, 24.3 g) are added, after which the suspension is degassed under nitrogen atmosphere for 10 min and the reaction is brought to 60°C for 1 h. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad and concentrated *in vacuo*. The residue is dissolved in EtOAc and an aq. extraction with sat. $NaHCO_3$ and EtOAc (3 x 150 mL) is performed. The combined organics are washed with sat. brine, dried (Na_2SO_4) and concentrated. Purification of the crude through column chromatography (silica, petroleum ether/EtOAc; 97.5:2.5 to 95:5) affords the desired product (amino-3-(2,2-difluorovinyl)-5-fluorobenzonitrile).

1.6.4. Step vi): 4-Amino-3-(2,2-difluoroethyl)-5-fluorobenzonitrile

[0243] A Parr reactor is charged with 4-amino-3-(2,2-difluorovinyl)-5-fluorobenzonitrile (1 eq, 200 mg) in anhydrous MeOH (10 mL) at room temperature, while nitrogen gas is bubbled through the mixture. Pd/C(10 wt%, 0.05 eq, 53 mg) is added, the cylinder is sealed and filled with hydrogen gas. A pressure of 3 bar is applied, and the reaction is stirred at room temperature over 2 days. The suspension is then

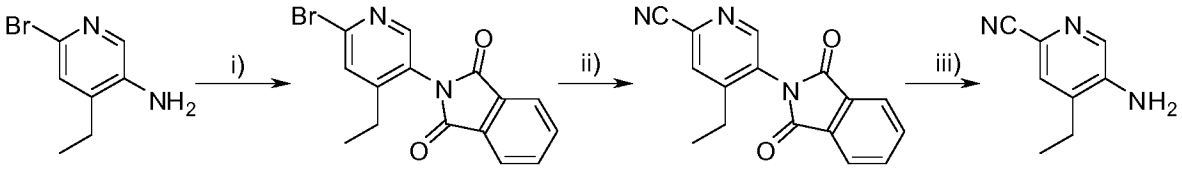
filtered over Celite pad, which is rinsed twice with MeOH. The filtrate is concentrated *in vacuo* and is used as such in the following step.

1.7. Intermediate 9



[0244] 4-Bromo-2-ethylaniline (4.96 mL, 35.0 mmol), the boronic acid (13 g, 42.0 mmol), $PdCl_2dppf$ (1.43 g, 1.75 mmol) and Cs_2CO_3 (34.2 g, 105 mmol) are heated at reflux in 1,4-dioxane (180 mL) and water (20 mL) for 18 h. The reaction mixture is cooled to room temperature and filtered through Celite, washed through with DCM and the organics are washed with water, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue is purified using column chromatography on silica gel and eluting with 10 - 20% EtOAc in isohexanes to give the desired compound.

1.8. Intermediate 10: 6-Cyano-4-ethyl-pyridin-3-ylamine



1.8.1. Step i): 2-(6-Bromo-4-ethyl-pyridin-3-yl)-isoindole-1,3-dione

[0245] A solution of 6-bromo-4-ethyl-pyridyn-3-yl-amine (1 eq) and isobenzofuran-1,3-dione (1 eq) in glacial acetic acid 246 mL) is heated at reflux for 6 h. The reaction mixture is cooled to room temperature and then acetic acid is evaporated *in vacuo*. After that, the residue is neutralized by $NaHCO_3$. The formed precipitate is filtered, washed with water and recrystallied from diethyl ether to afford the desired compound without further purification.

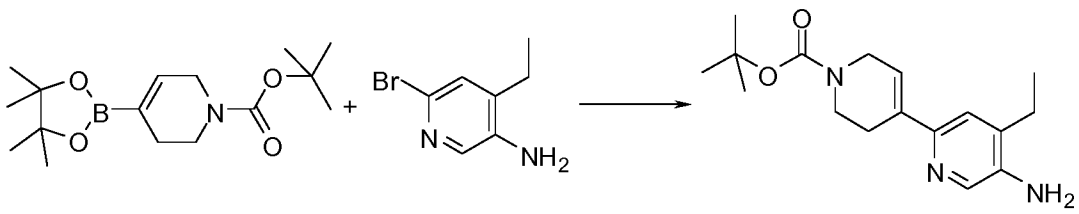
1.8.2. Step ii): 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-ethyl-pyridine-2-carbonitrile

[0246] A mixture of the compound obtained in step i) (1 eq), CuCN (1.2 eq) in drey NMP is heated to 150°C in a sealed tube for 22 min. The reaction mixture is poured into water and extracted with EtOAc. The organics are combined and dried over Na_2SO_4. After filtration, solvents are evaporated *in vacuo*. The resulting mixture is purified by colun chromatography and the desired product is obtained.

1.8.3. Step iii): 6-Cyano-4-ethyl-pyridin-3-ylamine

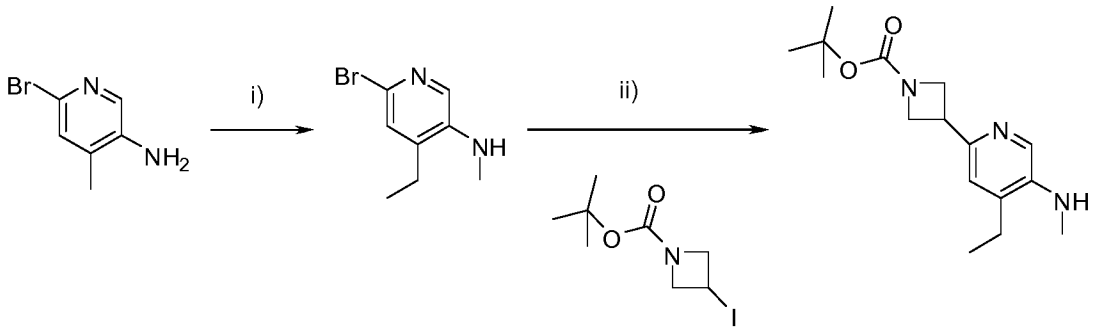
[0247] A reaction mixture of the compound obetained in step ii (1 eq) and NH_2NH_2 (3 eq) in dry EtOH is heated to 70°C for 30 min. After that, solvent is evaporated *in vacuo*. Water is added to the reaction mixture and then extraction with DCM followed. Organics are combined, dried over Na_2SO_4, filtered and evaporated under vacuo to obtain the desired compound.

1.9. Intermediate 11: 5-Amino-4-ethyl-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylic acid tert-butyl ester



[0248] Cs_2CO_3 (484.6 mg, 1.487 mmol) is added to the mixture of 6-bromo-4-ethyl-pyridin-3-ylamine (100.0 mg, 0.497 mmol) and 3,6-dihydro-2H-pyridine-1-tert-butoxycarbonyl-4-boronic acid, pinacol ester (184.0 mg, 0.595 mmol) in 1,4-dioxane (2.55 mL) and water (0.28 mL), and the mixture purged with argon before $PdCl_2$dppf (40.5 mg, 0.050 mmol) is added. Reaction mixture is then stirred and heated in a sealed tube at 100 °C overnight to yield the desired product.

1.10. Intermediate 12: 3-(4-Ethyl-5-methylamino-pyridin-2-yl)-azetidine-1-carboxylic acid tert-butyl ester



1.10.1. Step i): 2-Bromo-4-ethyl-5-methylaminopyridine

[0249] A solution of 6-bromo-4-ethyl-pyridin-3-ylamine (2.5 g; 12.43 mmol, 1 eq) is refluxed in triethylorthoformate (10 mL). The reaction mixture is then heated to reflux. After completion of the reaction, the triethylorthoformate is distilled off and the residue is dissolved in dry THF (10 mL). The resulting solution is added dropwise to a suspension $NaBH_4$ (3 eq; 1.41 g) and acetic acid (3 eq; 2.13 mL) in dry THF (30 mL). The mixture is then stirred for 20 h at room temperature, and the reaction is quenched by slow addition of 0.1 N NaOH. The organic substances are extracted with DCM, and the combined DCM extracts are dried and the solvent is evaporated. The obtained crude is purified by chromatography using 25 g normal phase silica SNAP column and cyclohexane/EtOAc solvent system (gradient 0-15 % of EtOAc in 20 CV) to yield the desired product.

[0250] MS $[M+H]^+$= 215.14

1.10.2. Step ii): 3-(4-Ethyl-5-methylamino-pyridin-2-yl)-azetidine-1-carboxylic acid tert-butyl ester

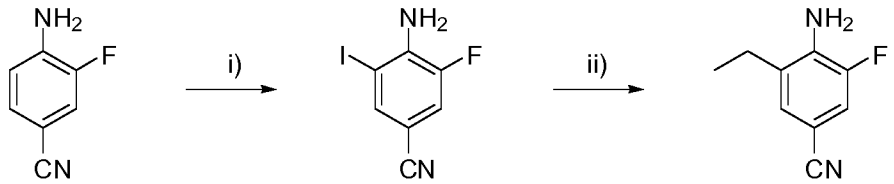
[0251] To a suspension of Rieke Zinc (2 eq; 611 mg, 12.24 mL; 50 mg/mL; suspension in dry THF) in dry DMA (4 mL) under argon atmosphere, heated at 65 °C is added a solution of tert-butyl 3-iodo-1-azetidine carboxylate (1.67 eq; 1.63 g/mL; 2.19 g; 1.35 mL) in 4 mL of dry DMA, dropwise over 30 min. THF is then distilled off and the resulting DMA suspension is heated at 65 °C for another 30 min. The

mixture is then allowed to cool to room temperature and is transfered to a mixture of 2-Bromo-4-ethyl-5-methylaminopyridine (1 g; 4.65 mmol; 1 eq), $PdCl_2$(dppf).DCM (0.03 eq; 114 mg) and CuI (0.06 eq, 53 mg) in dry DMA (8 mL) under argon atmosphere. The resulting reaction mixture is then stirred at 85 °C for 3 h, cooled to room temperature and quenched with 300 mL of saturated NH_4Cl water solution. The organic substances are extracted with EtOAc (twice, 300 mL used in total). The gathered EtOAc layer are dried over Na_2SO_4, and filtered over a celite pad. The solvent is evaporated and the resulting crude is purified by chromatography using 100 g normal phase silica SNAP coloumn and cyclohexane/EtOAc solvent system (gradient 20-80 % of EtOAc in 25 CV). The solvent from gathered fractions of appropriate composition is evaporated and the desired product is obtained.

[0252] MS $[M+H]^+$= 292.24

[0253] ^1H NMR ($CDCl_3$-d) δ/ppm: 7.92 (s, 1H), 6.90 (s, 1H), 4.18-4.28 (m, 2H), 4.03-4.16 (m, 2H), 3.72-3.82 (m, 1H), 3.52 (br. s., 1H), 2.92 (s, 3H), 2.43 (q, 2H), 1.37-1.48 (m, 9H), 1.23 (td, 3H)

1.11. Intermediate 13: 4-Amino-3-ethyl-5-fluorobenzonitrile



1.11.1. Step i): 4-Amino-3-fluoro-5-iodobenzonitrile

[0254] To a solution of iodine (1 eq, 18.6 g) in EtOH (350 mL) at room temperature is added silver sulfate (1 eq, 22.9 g) and 4-amino-3-fluorobenzonitrile (1 eq, 10.0 g). The suspension is stirred at room temperature for 1 h. The silver salts are then filtered off and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM and washed with aq. $Na_2S_2O_3$ (3 x 100 mL). The organic layer is washed with sat. brine and dried over anhydrous sodium sulfate to give the desired product.

1.11.2. Step ii): 4-Amino-3-ethyl-5-fluorobenzonitrile

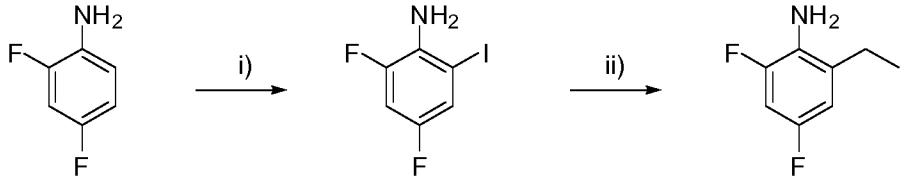
[0255] $PdCl_2$dppf (0.1 eq, 2.8 g) and Cs_2CO_3 (6 eq, 74.6 g) are dissolved in anhydrous DMF (250 mL) and the suspension is degassed under nitrogen atmosphere for 10 min. 4-Amino-3-fluoro-5-iodobenzonitrile (1 eq, 10.0 g) and triethylborane (1M in hexane, 1.3 eq, 50.0 mL) are added and the reaction is brought to 55°C for 2 h, using a condenser. The reaction mixture is then filtered over a Celite pad, which is washed with DCM. The filtrate is poured into water and extraction with DCM (3 x 100 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 90:10 to 80:20) to give the desired product.

1.11.3. Step ii): 5-Amino-4-chlorothiophene-2-carbonitrile

[0256] 5-Aminothiophene-2-carbonitrile (1 eq, 124 mg) is dissolved in anhydrous MeCN (10 mL) under nitrogen atmosphere. The reaction is cooled down to 0-5°C, while N-chlorosuccinimide (1 eq, 134 mg) is added at once. The reaction is kept stirring at 0-5°C for 3 h, after which LC-MS confirmed complete conversion into the desired product. The reaction mixture is concentrated under reduced pressure and the residue is partitioned between sat. $NaHCO_3$ and EtOAc. An aq. extraction with EtOAc (3 x 15 mL) is

performed and the combined organics are dried over anhydrous sodium sulfate. After concentration *in vacuo*, the obtained residue is purified via silica chromatography (DCM/NH_3 (7M in MeOH); 100:0 to 95:5) to deliver the desired product.

1.12. Intermediate 14: 2-Ethyl-4,6-difluoroaniline



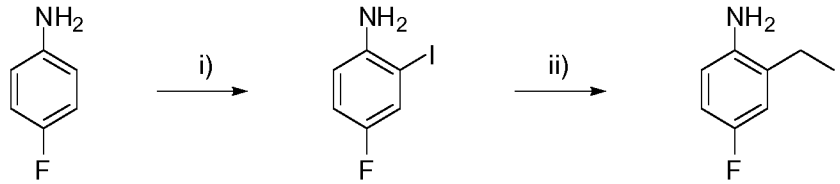
1.12.1. Step i): 2,4-Difluoro-6-iodoaniline

[0257] Iodine (1 eq, 19.7 g) is dissolved in EtOH (350 mL) at room temperature and 2,4-difluoroaniline (1 eq, 8 mL) and silver sulfate (1 eq, 24.1 g) are added. The suspension is stirred at room temperature overnight. After completion of the reaction as seen by LC-MS, the silver salts are filtered off and the filtrate is concentrated *in vacuo*. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$ (3 x 100 mL). The organic layer is washed with sat. brine and dried over anhydrous sodium sulfate to give the desired product after column chromatography (silica, petroleum ether/EtOAc; 100:0 to 95:5).

1.12.2. Step ii): 2-Ethyl-4,6-difluoroaniline

[0258] $PdCl_2dppf$ (0.1 eq, 3.2 g), Cs_2CO_3 (6 eq, 76.7 g) and 2,4-difluoro-6-iodoaniline (1 eq, 10.0 g) are dissolved in anhydrous DMF (250 mL) and the suspension is degassed under nitrogen atmosphere for 10 min. Triethylborane (1M in hexane, 1.3 eq, 51.0 mL) is added and the reaction is heated to 55°C, using a condenser. The reaction mixture is kept at the same temperature, while stirring for 6 h. Upon completion of the reaction, as seen by LC-MS, the suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured into water and extraction with DCM (3 x 100 mL) is performed. The combined organics are washed with sat. brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 90:10) to give the end product.

1.13. Intermediate 15: 2-Ethyl-4,6-difluoroaniline



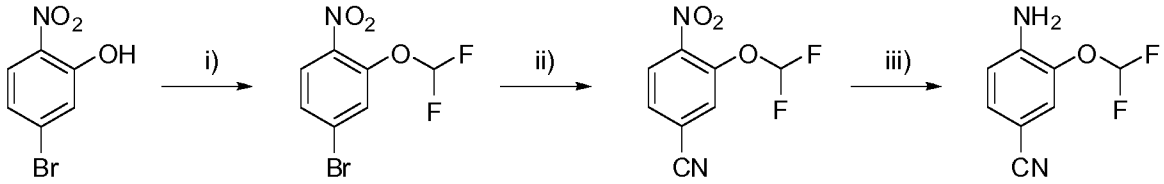
1.13.1. Step i): 4-Fluoro-2-iodoaniline

[0259] Iodine (1 eq, 11.4 g) is dissolved in EtOH (180 mL) at room temperature in a 250 mL round bottom flask and 4-fluoroaniline (1 eq, 4.3 mL) and silver sulfate (1 eq, 14.0 g) are added. After overnight stirring of the suspension at room temperature, the silver salts are filtered off and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$ (3 x 50 mL). The organic layer is washed with sat. brine, dried over Na_2SO_4 and purified via silica chromatography (petroleum ether/EtOAc; 100:0 to 80:20) to give the desired product.

1.13.2. Step ii): 2-Ethyl-4-fluoroaniline

[0260] $PdCl_2dppf$ (0.1 eq, 865 mg), Cs_2CO_3 (6 eq, 20.7 g) and 4-fluoro-2-iodoaniline (1 eq, 2.51 g) are dissolved in dry DMF (100 mL) in a 250 mL round bottom flask. The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of triethylborane (1M in hexane, 1.3 eq, 14.0 mL). The reaction is heated to 55°C for 2 h, using a condenser. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured into water and extraction with DCM (3 x 50 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 90:10) to give the desired product.

1.14. Intermediate 16: 4-Amino-3-difluoromethoxybenzonitrile



1.14.1. Step i): 4-Bromo-2-difluoromethoxy-1-nitrobenzene

[0261] 5-Bromo-2-nitrophenol (1 eq, 8.0 g) and potassium hydroxide (15 eq, 31.0 g) are dissolved in a 1:1 solution of H_2O and MeCN (240 mL). The reaction is cooled down to -25°C, after which diethyl (bromodifluoromethyl) phosphonate (1 eq, 6.5 mL) is carefully added. The cooling bath is removed and the reaction is left stirring for 1 h, while slowly warming up to room temperature. Another 0.6 eq of the phosphonate (4.0 mL) are added at -25°C, after which the cooling bath is removed and the reaction mixture is stirred for 90 min at room temperature. After completion of the reaction as shown by LC-MS, the mixture is diluted with Et_2O and sat. $NaHCO_3$. Extraction with Et_2O (3 x 100 mL) is performed. The combined organics are washed with sat. brine and dried over anhydrous Na_2SO_4. Purification of the crude through column chromatography (silica, cyclohexane/DCM; 100:0 to 90:10) yields the desired product.

1.14.2. Step ii): 3-Difluoromethoxy-4-nitrobenzonitrile

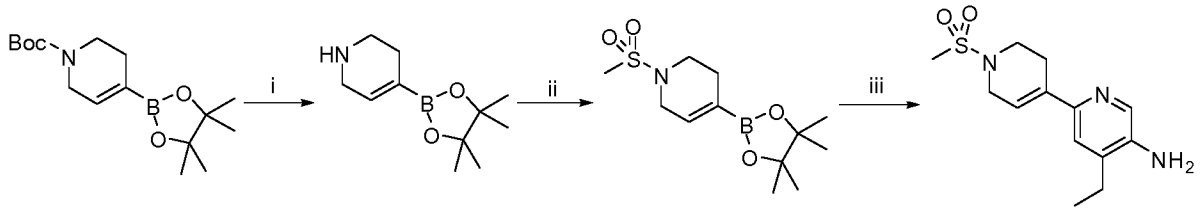
[0262] $Pd(PPh_3)_4$ (0.1 eq, 43 mg), zinc cyanide (1.05 eq, 48 mg) and 4-bromo-2-difluoromethoxy-1-nitrobenzene (1 eq, 100 mg) are dissolved in anhydrous DMF (1.5 mL) in a 10 mL microwave tube. The suspension is degassed under nitrogen atmosphere for 10 min, after which the reaction is brought to 150°C for 3 min under microwave irradiation (absorption level: high). The reaction mixture is cooled down and poured into water. Extraction with EtOAc (3 x 10 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue is used as such in the following reduction reaction.

1.14.3. Step iii): 4-Amino-3-difluoromethoxybenzonitrile

[0263] Crude 3-difluoromethoxy-4-nitrobenzonitrile (1 eq, 0.37 mmol) is dissolved in dry MeOH (2 mL) in a 10 mL tube. Zinc (5 eq, 122 mg), ammonium chloride (0.1 eq, 2 mg) and formic acid (0.5 mL) are successively added, after which the reaction is heated to 65°C for 1 h. LC-MS confirmed complete consumption of the starting material. The reaction mixture is cooled down and diluted with sat. $NaHCO_3$

and DCM. An aq. extraction with DCM (3 x 15 mL) is performed and the combined organics are dried over anhydrous sodium sulfate. After concentration under reduced pressure, the obtained residue is used as such in the following Buchwald reaction.

1.15. Intermediate 17: 4-Amino-3-difluoromethoxybenzonitrile



1.15.1. Step i : 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,6-tetrahydro-pyridine

[0264] 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (1.0 eq, 2.0 g) is treated with a solution of hydrochloric acid in dioxane (4.0M, 10 mL) and the resulting mixture is stirred at room temperature for 1 h. When the reaction is complete, the mixture is concentrated *in vacuo* to yield the desired product.

1.15.2. Step ii : 1-Methanesulfonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,6-tetrahydro-pyridine

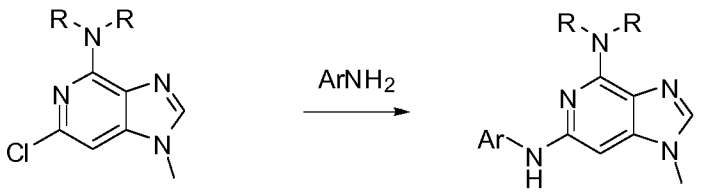
[0265] To a solution of 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,6-tetrahydro-pyridine (1.0 eq, 1.3 g) and DIPEA (3 eq, 3.4 mL) in DCM (10 mL) at 0 °C is added a solution of mesylchloride (1.1 eq, 550 µL) in DCM (5 mL) and the resulting mixture is stirred at room temperature for 1 h, then diluted with DCM and water. The two phases are separated and the organic layer is washed with brine, filtered through a phase separator and concentrated to afford the desired product.

1.15.3. Step iii : 4-Ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamine

[0266] A degassed mixture of 6-bromo-4-ethyl-pyridin-3-ylamine (1 eq, 200 mg), 1-methanesulfonyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,6-tetrahydro-pyridine (1.2 eq, 345 mg), K_2CO_3 (3.0 eq, 410 mg) and Pd(dppf)CL_2 (0.05 eq, 40 mg) in a mixture of water and 1,4-dioxane (4/1 mL) is heated at 80 °C for 1 h. The reaction mixture is diluted with ethyl acetate and filtered through a celite pad. Solids are thoroughly washed with ethyl acetate. The filtrate is concentrated. The residue is diluted in DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated to afford the desired product.

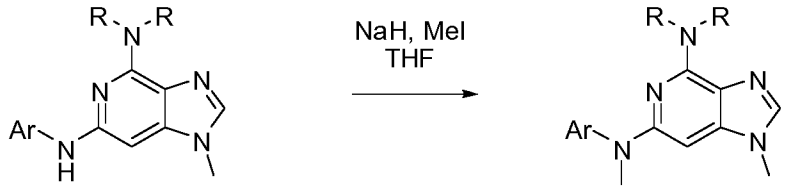
Example 2. General synthetic methods

2.1. Method A: Buchwald reaction



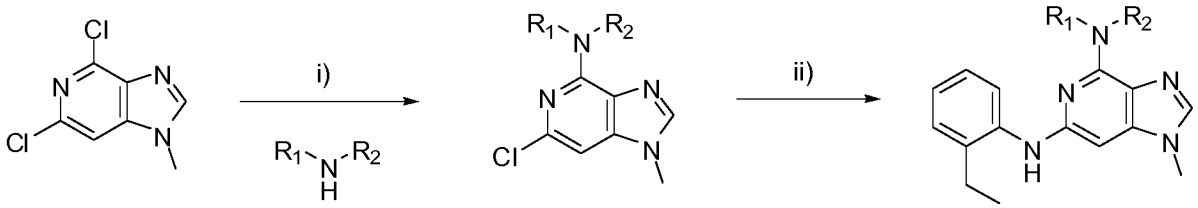
[0267] A mixture of the aniline (1.1 eq), the amino-imidazole derivative (1 eq), Cs_2CO_3 (2.5 eq), Xphos (0.3 eq) and $Pd_2(dba)_3$ (0.1 eq) in dry dioxane (4 mL/0.25 mmol Intermediate 8) is degassed under nitrogen atmosphere for 10 min while sonicating. The suspension is brought to 100°C and is kept stirring at this temperature until completion of the reaction. Water is added and the reaction mixture is extracted with DCM. The combined organics are dried, concentrated and the residue is purified by silica chromatography to give the desired compound.

2.2. Method B: N-methylation



[0268] To a solution of amino-imidazole derivative (1 eq), dissolved in anhydrous THF (1 mL/0.25 mmol intermediate 9), is added NaH (60% in mineral oil, 1.5 eq). The reaction is stirred at room temperature for 15 min, after which methyl iodide (1.1 eq) is added dropwise. After completion of the reaction as seen by LC-MS, the mixture is diluted with water and DCM and extraction is performed. The organic layers are combined, dried over sodium sulfate and concentrated under reduced pressure. The crude is purified through column chromatography to give the desired compound.

2.3. Method C: General procedure: SnAr and Buchwald



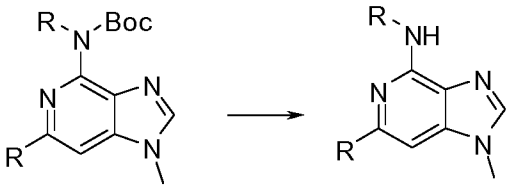
2.3.1. Step i)

[0269] 4,6-Dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (300 mg, 1.49 mmol) and the amine (11.9 mmol) in EtOH (7 mL) are stirred and heated to 150 °C using microwave irradiation for 80 min. The reaction mixture is cooled to room temperature, concentrated *in vacuo* and purified by column chromatography using silica gel.

2.3.2. Step ii)

[0270] To stirred degassed (N_2) 1,4-dioxane (4 mL) is added the product from step 1 (0.52 mmol), 2-ethylaniline (70 mg, 0.58 mmol), $Pd_2(dba)_3$ (24 mg, 0.026 mmol), Xphos (25 mg, 0.052 mmol) and sodium tert-butoxide (75 mg, 0.78 mmol). The reaction mixture is heated to 100 °C for 1 d, cooled to room temperature, filtered through Celite and washed through with DCM. The reaction mixture is washed with water and the layers are separated and the aqueous layer further extracted with DCM. The organics are combined, dried (hydrophobic filter) and concentrated *in vacuo* and the resulting residue is purified by preparative HPLC.

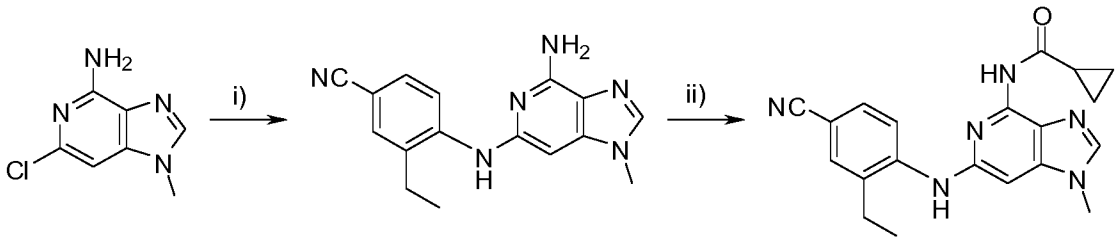
2.3.3. Method D: Boc deprotection



[0271] A mixture of Boc protected imidazopyridine in TFA is stirred at room temperature for 1 h. The mixture is concentrated and the residue is purified preparative HPLC

Example 3. Illustrative compounds of the invention.

3.1. Compound 1: N-(6-(4-cyano-2-ethylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



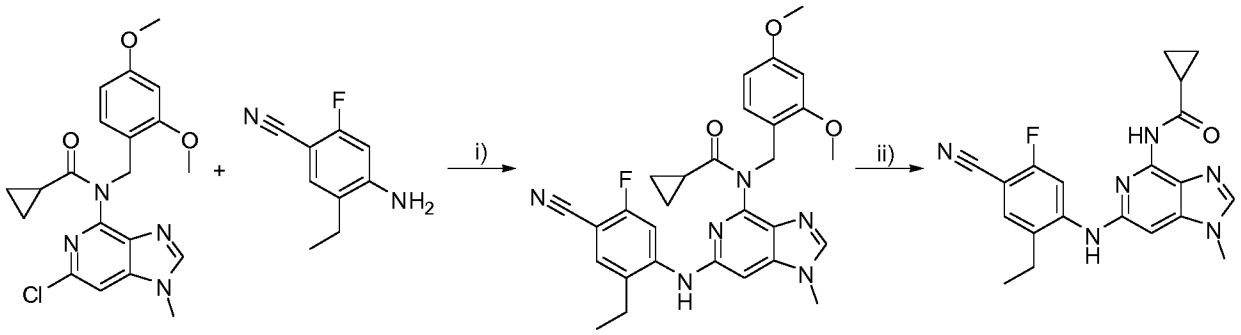
3.1.1. Step i): 4-(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-3-ethyl-benzonitrile

[0272] To stirred degassed (N_2) 1,4-dioxane (4 mL) is added intermediate 3 (0.52 mmol), 4-cyano-2-ethylaniline (70 mg, 0.58 mmol), $Pd_2(dba)_3$ (24 mg, 0.026 mmol), BINAP (0.052 mmol) and Cs_2CO_3 (1.04 mmol). The reaction mixture is heated to 110 °C for 16 h in a sealed tube, cooled to room temperature, filtered through Celite and washed through with DCM. The reaction mixture is washed with water and the layers are separated and the aqueous layer further extracted with DCM. The organics are combined, dried (hydrophobic filter) and concentrated *in vacuo* and the resulting residue is purified by preparative HPLC.

3.1.2. Step ii): N-(6-(4-cyano-2-ethylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0273] Compound obtained in step i) (1 eq, 500 mg) is dissolved in anhydrous DCM (4 mL) in a sealed 10 mL tube, together with cyclopropanecarboxylic acid chloride (1.5 eq, 205 µL). Dry pyridine (2 mL) is added and the reaction is heated to 45°C for 1 h. After completion of the reaction as shown by LC-MS, the reaction is diluted with water (25 mL) and DCM (50 mL). The organic layer is successively washed with 25 mL of sat. $NaHCO_3$ and 25 mL of sat. brine. Drying over anhydrous sodium sulfate, concentration *in vacuo* followed by purification by preparative HPLC yielded the desired compound.

3.2. Compound 2: N-(6-(4-cyano-2-ethyl-5-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.2.1. Step i)

[0274] Preparation: Method A

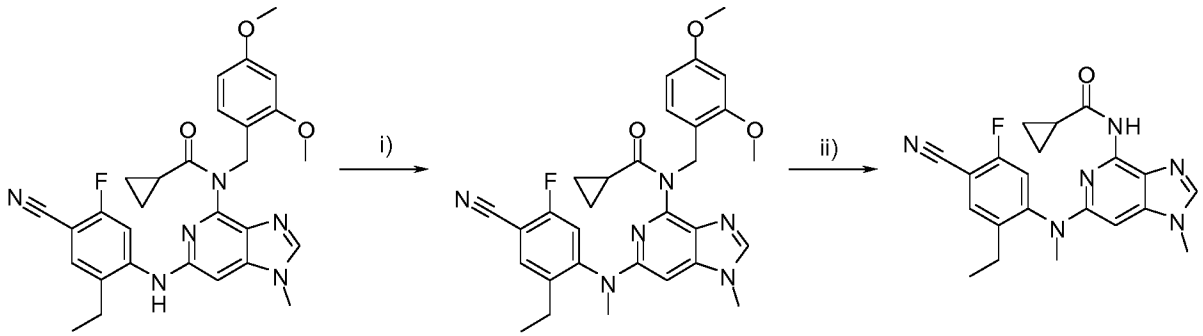
3.2.2. Step ii)

[0275] To a solution of Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-5-fluoro-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide (26 mg, 0.049 mmol) in DCM (1 mL) is added trifluoro acetic acid (189.5 µL, 2.460 mmol) The resulting solution is stirred at room temperature for four h. The mixture is concentrated *in vacuo*. The sample is loaded onto an SCX (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) column in a mixture of DCM and MeOH. MeOH (20mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (20 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0276] ^{1}H NMR (DMSO-d_6) : 10.55 (s, 1H), 8.77 (d, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 7.48 (d, 1H), 7.17 (s, 1H), 3.77 (s, 3H), 2.72 (q, 2H), 2.06-2.21 (m, 1H), 1.18 (t, 3H), 0.74-0.87 (m, 4H)

[0277] LC-MS: m/z $(M+H)^+$ 379.19

3.3. Compound 3: N-(6-((4-cyano-2-ethyl-5-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



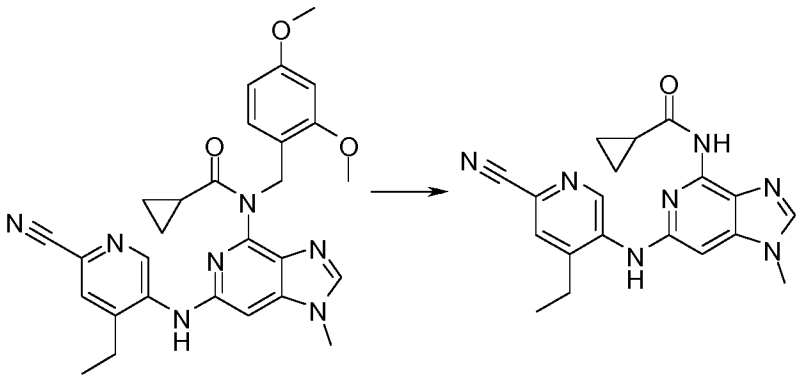
3.3.1. Step i)

[0278] Preparation: Method B

3.3.2. Step ii)

[0279] Same method as for Compound 2, Step ii)

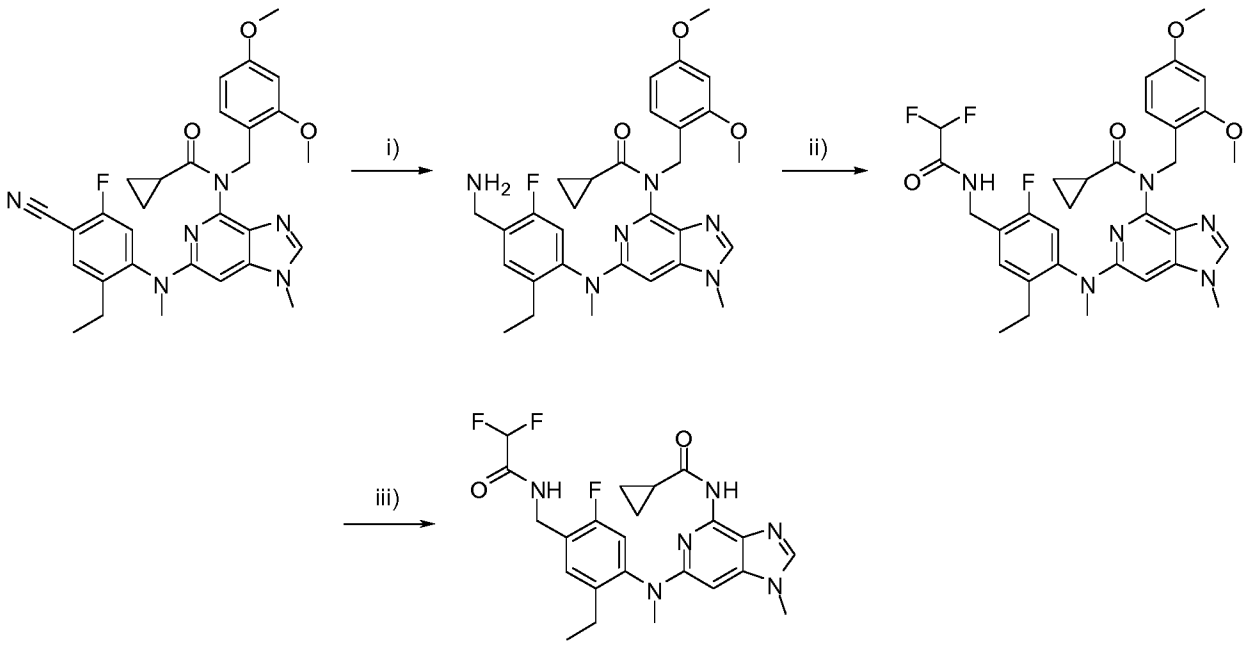
3.4. Compound 4: N-(6-(6-cyano-4-ethylpyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



[0280] To a solution of Cyclopropanecarboxylic acid [6-(6-cyano-4-ethyl-pyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide (obtained by method A) (40.6 mg, 0.070 mmol) in DCM (1 mL) is added TFA (305.7 µL, 3.968 mmol) The resulting solution is stirred at room temperature for 4 h and the mixture is concentrated *in vacuo*. The sample is loaded onto an SCX (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) column in a mixture of DCM and MeOH. MeOH (20mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (20 mL). The filtrate is concentrated *in vacuo* to yield the desired product.

[0281] ^{1}H NMR (DMSO-d_6) : 10.42 (s, 1H), 9.62 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.71 (s, 1H), 7.05 (s, 1H), 3.76 (s, 3H), 2.73 (q, 2H), 2.09 (d, 1H), 1.19 (t, 3H), 0.80 (t, 4H).

3.5. Compound 5: N-(6-((4-((2,2-difluoroacetamido)methyl)-2-ethyl-5-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.5.1. Step i)

[0282] To a solution of Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-5-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (synthesis described above) (93.4 mg, 0.172 mmol) in MeOH (2 mL) is added Nickel(II) Chloride 6-hydrate (40.9 mg,

0.172 mmol) and TFA (106 µL, 1.376 mmol). The mixture is cooled at 0°C and sodium borohydride (52.1 mg, 1.376 mmol) is added. The resulting solution is allowed to warm up to room temperature and stirred over 2 days. The reaction mixture is filtered through celite and the filtrate concentrated *in vacuo*. EtOAC and NaOH (2 M) solution are added. The aqueous layer is extracted with EtOAc and the combined organics are dried over anhydrous Na_2SO_4 and evaporated to yield 80.8 mg of the crude product. The sample is purified on BIOTAGE SP1 purification device, by chromatography, using 10 g normal phase silica SNAP column and DCM:MeOH solvent system (gradient 0-50% of MeOH in 15 CV). Solvent from gathered fractions of appropriate composition is evaporated to yield the crude desired product.

[0283] LC-MS: m/z = 547.26 $[M+H]^+$

3.5.2. Step ii)

[0284] Difluoroacetic anhydride (11.6 µL, 0.093 mmol) is added to a solution of Cyclopropanecarboxylic acid {6-[(4-aminomethyl-2-ethyl -5-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo [4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (50.9 mg, 0.093 mmol) in dry DCM (1 mL) and the reaction mixture stirred at room temperature for 1 h. The reaction mixture is concentrated under reduced pressure to afford the raw product as orange oil.The sample is purified on BIOTAGE SP1 purification device, by chromatography, using 10 g normal phase silica SNAP column and DCM:MeOH solvent system (gradient 0-50% of MeOH in 20 CV). Solvent from gathered fractions of appropriate composition is evaporated. The crude product is isolated.

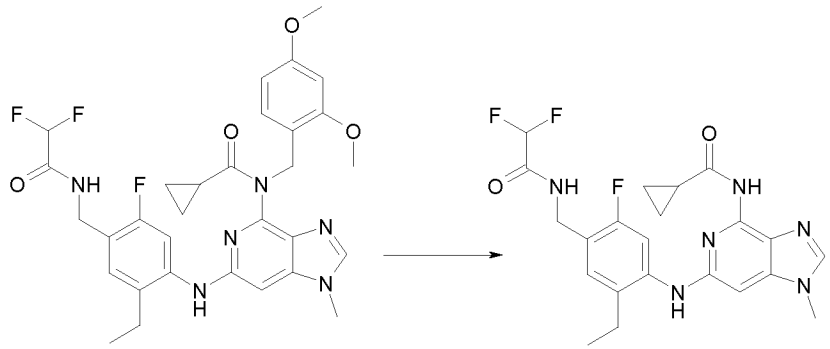
[0285] LC-MS, m/z = 625.24 $[M+H]^+$

3.5.3. Step iii)

[0286] To a solution of Cyclopropanecarboxylic acid [6-({4-[(2,2-difluoro-acetylamino)-methyl]-2-ethyl-5-fluoro-phenyl}-methyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridine-4-yl]-(2,4-dimethoxy-benzyl)-amide (32.7 mg, 0.052 mmol) in DCM (1 mL) is added **2** (202 µL, 2.617 mmol) The resulting solution is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and the sample is loaded onto an SCX (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) column in a mixture of DCM and MeOH. MeOH (20mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (20 mL). The filtrate is concentrated *in vacuo* to give the crude desired product.

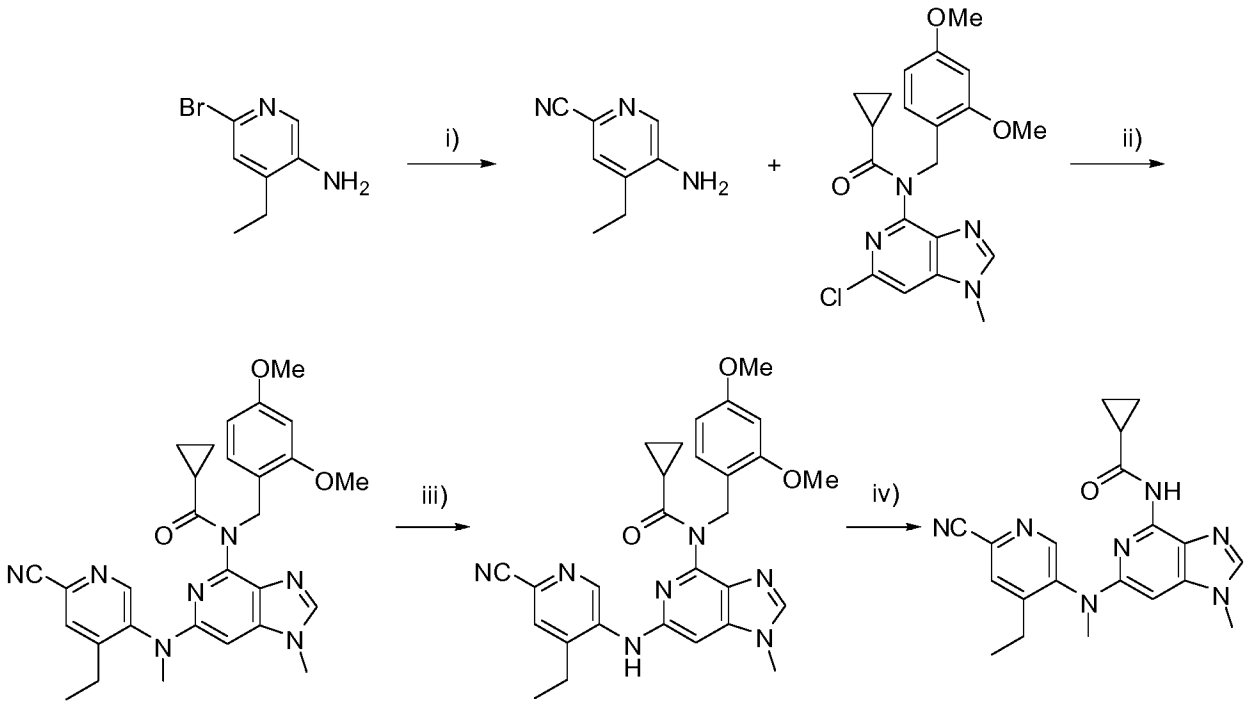
[0287] ^1H NMR (DMSO-d_6) : 9.70 (br. s., 1H), 9.33 (br. s., 1H), 7.92 (s, 1H), 7.29 (d, 1H), 7.06 (d, 1H), 6.10-6.49 (m, 1H), 6.06 (s, 1H), 5.74 (s, 1H), 4.40 (d, 2H), 3.61 (s, 3H), 2.39 (q, 2H), 2.26 (br. s., 1H), 1.04 (t, 3H), 0.76 (br. s., 2H), 0.63 (br. s., 2H). LC-MS: m/z = 475.17 $[M+H]^+$

3.5.4. Compound 6: N-(6-(4-((2,2-difluoroacetamido)methyl)-2-ethyl-5-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



[0288] Same method as the one described for Compound 5 without the methylation step

3.6. Compound 7: N-(6-((6-cyano-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.6.1. Step i): 5-Amino-4-ethyl-pyridine-2-carbonitrile

[0289] A mixture of 6-bromo-4-ethyl-pyridin-3-ylamine (1.0 eq, 500 mg) and $Zn(CN)_2$ (1.0 eq, 292 mg) in dry DMA (2.5 mL) and dry DMF (7.5 mL) is heated at 90 °C. After 15 min, $Pd(PPh_3)_4$ (0.1 eq, 289 mg) is added and the heating continued for 24 h. Once cooled down, the mixture is diluted with EtOAc, washed with aq. sat. $NaHCO_3$, brine, dried and concentrated. Silica chromatography (EtOAc/petrol ether; 20:80 to 50:50) affords the desired compound.

3.6.2. Step ii): Cyclopropanecarboxylic acid [6-(6-cyano-4-ethyl-pyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide

[0290] A degassed mixture of the amine (1.0 eq, 91 mg), the chloroaryl (1.0 eq, 250 mg), Pd_2dba_3 (0.1 eq, 55 mg), XPhos (0.3 eq, 99 mg) and Cs_2CO_3 (2.5 eq, 505 mg) in dry dioxane (5 mL) is heated at 100°C

for 18 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. This mixture is used in the next step without further purification.

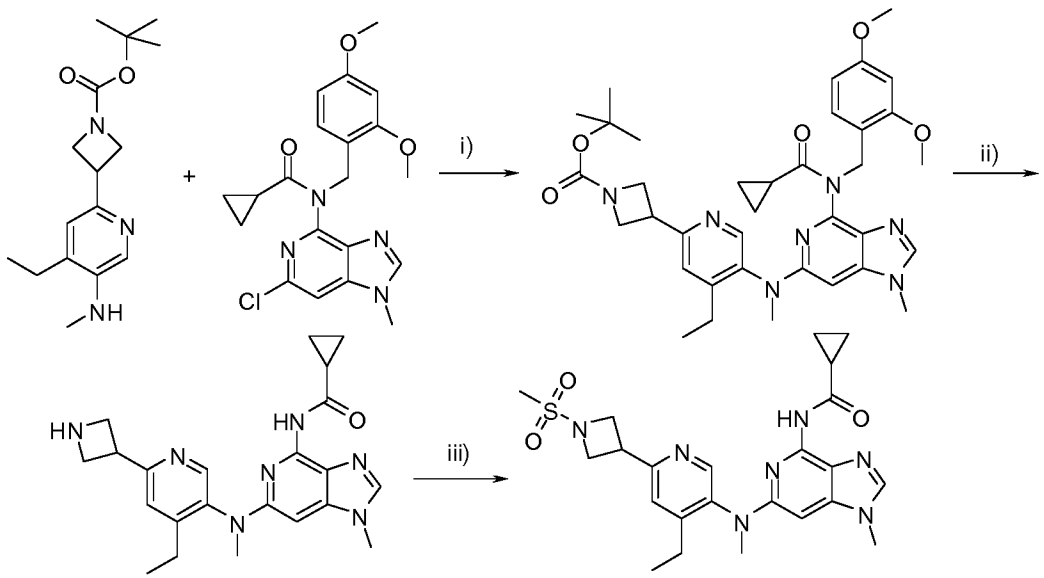
3.6.3. Step iii): Cyclopropanecarboxylic acid {6-[(6-cyano-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide

[0291] To the crude amine in THF (5 mL) is added NaH (2 eq, 50 mg). After 5 min, MeI (2 eq, 117 µL) is added and the mixture is stirred at room temperature for 2 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used in the next step without further purification.

3.6.4. Step iv): N-(6-((6-cyano-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0292] TFA (2 mL) is added to the crude DMB-protected compound in DCM (4 mL) and stirred at 50 °C for 2 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Silica chromatography (EtOAc/petrol ether; 80:20 to 100:0 then MeOH/EtOAc; 1:99 to 3:97) to afford the desired compound.

3.7. Compound 8: N-(6-((4-ethyl-6-(1-(methylsulfonyl)azetidin-3-yl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.7.1. Step i)

[0293] Preparation: method A

3.7.2. Step ii)

[0294] TFA (433.5 µL, 5.627 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(6-azetidin-3-yl-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (73.8 mg, 0.113 mmol) in DCM (1.5 mL) and the solution stirred at room temperature overnight. The reaction mixture is then loaded onto an SCX column (600 mg, 3.0 mmol/g, preconditioned with 25 mL of MeOH). MeOH (25 mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (25 mL). The filtrate is concentrated *in vacuo* to give desired product.

[0295] LC-MS: m/z = 406.20 $[M+H]^+$.

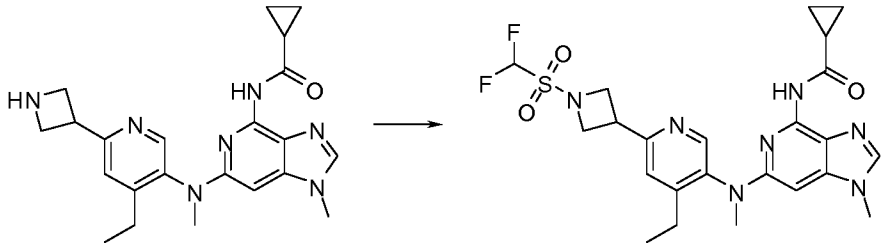
3.7.3. Step iii)

[0296] Pyridine (13.22 µL, 0.163 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(6-azetidin-3-yl-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (22.1 mg, 0.054 mmol) and methanesulfonyl chloride (4.64 µL, 0.060 mmol) in DCM (0.50 mL) and the reaction mixture stirred at room temperature for 7 h. To the reaction mixture additional methanesulfonyl chloride (2.32 µL, 0.030 mmol) and pyridine (13.22 µL, 0.163 mmol) are added. Stirring is continued at room temperature overnight. The reaction mixture is concentrated under reduced pressure to afford the crude product. The sample is loaded and pre-purified on silica column., the desired product is isolated, further partitioned between water (15 mL) and DCM (3 × 10 mL). The combined organic layers are washed with sat $NaHCO_3$ (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired product.

[0297] ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 0.53 – 0.63 (m, 2H), 0.70 – 0.78 (m, 2H), 1.08 (t, 3H), 2.16 – 2.29(m, 1H), 2.43 (q, 2H), 3.07 (s, 3H), 3.33 (s, 3H), 3.65 (s, 3H), 3.96 – 4.08 (m, 1H), 4.09 – 4.23 (m, 4H), 6.17(s, 1H), 7.35 (s, 1H), 7.95 (s, 1H), 8.38 (s, 1H), 9.68 (s, 1H).

[0298] LC-MS : m/z = 484.16 $[M+H]^+$.

3.8. Compound 9: N-(6-((6-(1-(difluoromethylsulfonyl)azetidin-3-yl)-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

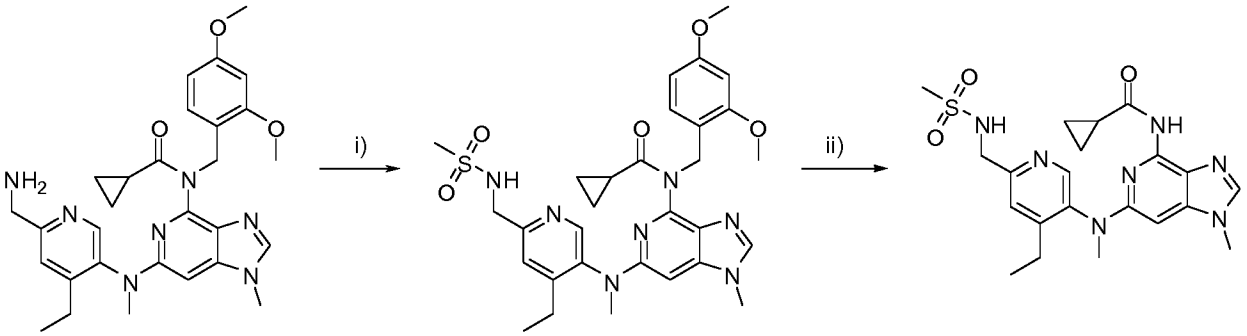


[0299] Pyridine (13.22 µL, 0.163 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(6-azetidin-3-yl-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (synthesis described for compound 101) (22.1 mg, 0.054 mmol) and difluoromethanesulfonyl chloride (5.32 µL, 0.060 mmol) in dry DCM (0.50 mL) and the reaction mixture stirred at room temperature for 7 h. To the reaction mixture difluoromethanesulfonyl chloride (2.66 µL, 0.030 mmol) and pyridine (13.22 µL, 0.163 mmol) are added. Stirring is continued at room temperature overnight. Reaction mixture is concentrated under reduced pressure. To the residue water (15 mL) is added and extracted with DCM (3 × 10 mL). The combined organic layers are washed with sat $NaHCO_3$ (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. The sample is loaded and purified on silica column to yield the desired product.

[0300] ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 0.53 – 0.64 (m, 2H), 0.70 – 0.79 (m, 2H), 1.08 (t, 3H), 2.15 – 2.30 (m, 1H), 2.43 (q, 2H), 3.33 (s, 3H), 3.65 (s, 3H), 4.09 – 4.25 (m, 1H), 4.35 – 4.50 (m, 1H), 6.18 (s, 1H), 7.22 (s, 1H), 7.34 (s, 1H), 7.98 (s, 1H), 8.42 (s, 1H).

[0301] LC-MS: m/z = 520.14 $[M+H]^+$,

3.9. Compound 10 : N-(6-((4-ethyl-6-(methylsulfonamidomethyl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



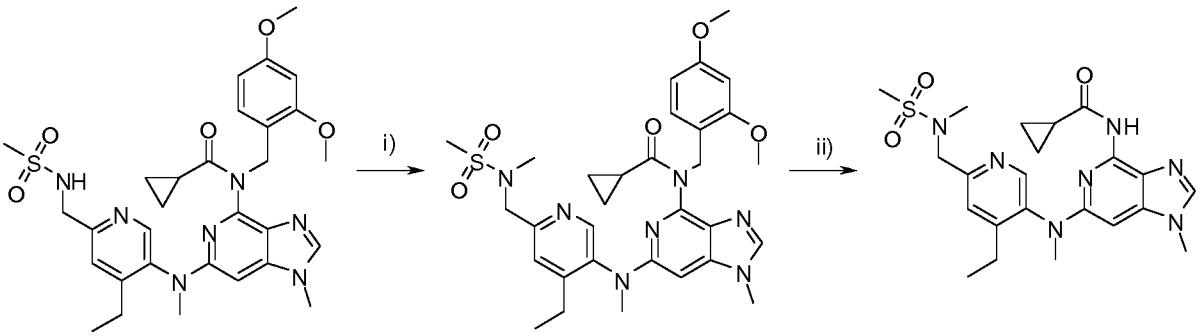
3.9.1. Step i)

[0302] Methane sulfonylchloride (8 µL, 0.103) is added to a solution of Cyclopropanecarboxylic acid {6-[(6-aminomethyl-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (synthesis described above) (45.7 mg, 0.086 mmol) in DCM:Pyridine (3 mL:1.5 mL) and the reaction mixture is stirred at room temperature overnight after which the solvent is evaporated from reaction mixture. The residue is diluated with water (15 mL) and extracted with DCM (3x15 mL). The combined organic extracts are dried over anhydrous Na_2SO_4 and evaporated to yield the the crude product.

3.9.2. Step ii)

[0303] To a solution of Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(6-{[4-ethyl-6-(methanesulfonylamino-methyl)-pyridin-3-yl]-methyl-amino}-1-methyl-1H-imidazo [4,5-c]pyridin-4-yl)-amide (52.3 mg, 0.086 mmol) in DCM (1 mL) is added TFA (530 µL, 6.884 mmol) The resulting solution is stirred at room temperature overnight. According to LC-MS the reaction is complete (m/z $(M+H)^+$ 458.14). The mixture is concentrated *in vacuo* and the sample is loaded onto an SCX (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) column in a mixture of DCM and MeOH. MeOH (20mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (20 mL). The filtrate is concentrated *in vacuo* to give 34.5 mg of crude product. The sample is purified again on 5 g silica gel column on SolidPrep purification system in DCM:MeOH = 20:1 solvent system (isocratic). After evaporation of solvent 16 mg of product is isolated.

3.10. Compound 11: N-(6-((4-ethyl-6-((N-methylmethylsulfonamido)methyl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.10.1. Step i)

[0304] To a solution of Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(6-{[4-ethyl-6-(methanesulfonylamino-methyl)-pyridin-3-yl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide (synthesis described above) (26.5 mg, 0.044 mmol) in dry DMF (1 mL) cooled at 0°C is added NaH, 60% in mineral oil (3.5 mg, 0.087 mmol) The resulting solution is stirred for 20 min. Then is added Methyl iodide (3.3 µL, 0.523 mmol) and the mixture is stirred for 2 h. The reaction mixture is quenched with 10 mL water and extracted with DCM (3 x 10 mL). The combined organic extracts are dried over anhydrous Na_2SO_4 and evaporated to yield the crude product.

[0305] LC-MS m/z = 622.24 $[M+H]^+$

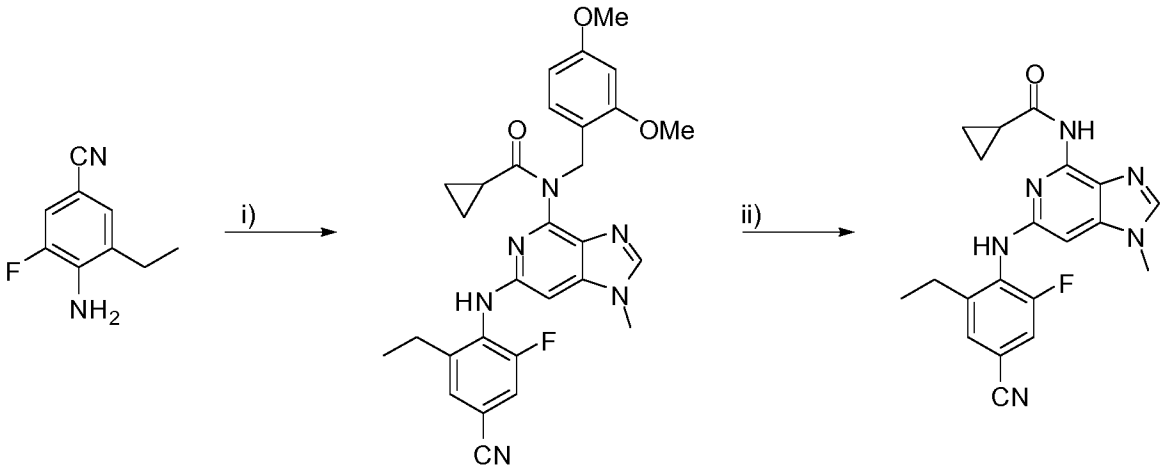
3.10.2. Step ii)

[0306] To a solution of Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-[6-({4-ethyl-6-[(methanesulfonyl-methyl-amino)-methyl]-pyridin-3-yl}-methyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-amide (29 mg, 0.046 mmol) in DCM (1 mL) is added TFA (289.4 µL, 3.731 mmol). The resulting solution is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and loaded onto an SCX column (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) in a mixture of DCM and MeOH. MeOH (15 mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (15 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0307] ^1H NMR (DMSO-d_6): 9.67 (br. s., 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.36 (s, 1H), 6.17 (s, 1H), 4.37 (s, 2H), 3.65 (s, 3H), 3.00 (s, 3H), 2.82 (s, 3H), 2.41-2.47 (m, 2H), 2.22 (br. s., 1H), 1.09 (t, 3H), 0.73 (d, 2H), 0.52-0.65 (m, 2H)

[0308] LC-MS m/z = 472.12 $[M+H]^+$

3.11. Compound 12: Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide



3.11.1. Step i): Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxybenzyl)amide

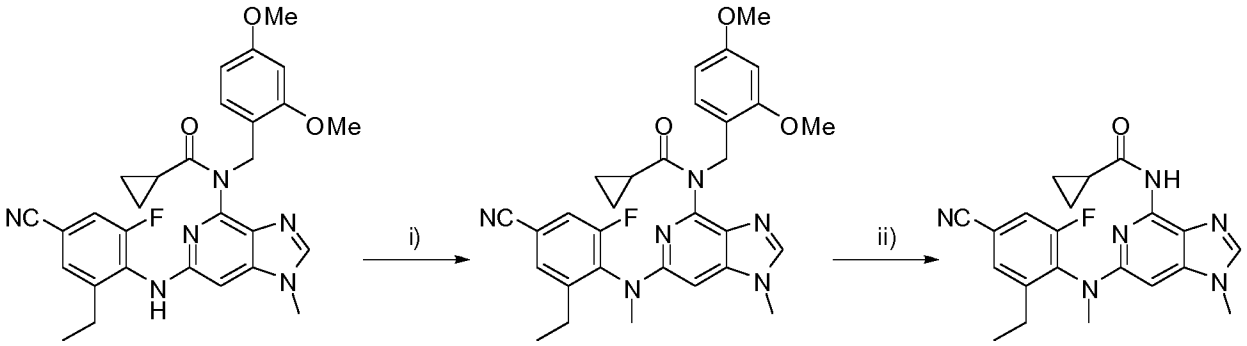
[0309] Prepared via method A using 4-Amino-3-ethyl-5-fluorobenzonitrile (Intermediate 23) (1.1 eq, 45 mg) to give the desired compound after 2 h. The organic residue is purified by silica chromatography (DCM/MeOH/EtOAc; 100:0:0 over 50:0:50 and 0:0:100 to 0:5:95) to afford the desired compound.

3.11.2. Step ii): Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

[0310] Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxybenzyl)amide (1 eq, 68 mg) is dissolved in 2 mL anhydrous DCM. TFA (35 eq, 334 µL) is carefully added at room temperature, after which the solution is left stirring overnight. After completion of the reaction the reaction mixture is extracted with sat. $NaHCO_3$ and DCM (3 x 20 mL). After drying over anhydrous sodium sulfate and concentration *in vacuo* the desired product is obtained.

[0311] ^1H NMR (300 MHz, DMSO-d_6) 10.46 (1 H, s), 8.64 (1 H, d), 8.52 (1 H, s), 7.70 (1 H, d), 7.61 (1 H, s), 6.60 (1 H, s), 3.78 (3 H, s), 2.67 (2 H, q), 2.16 (1 H, br. s), 1.12 (3 H, t), 0.84 (2 H, s), 0.80-0.75 (2 H, m).

3.12. Compound 13: Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



3.12.1. Step i): Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide

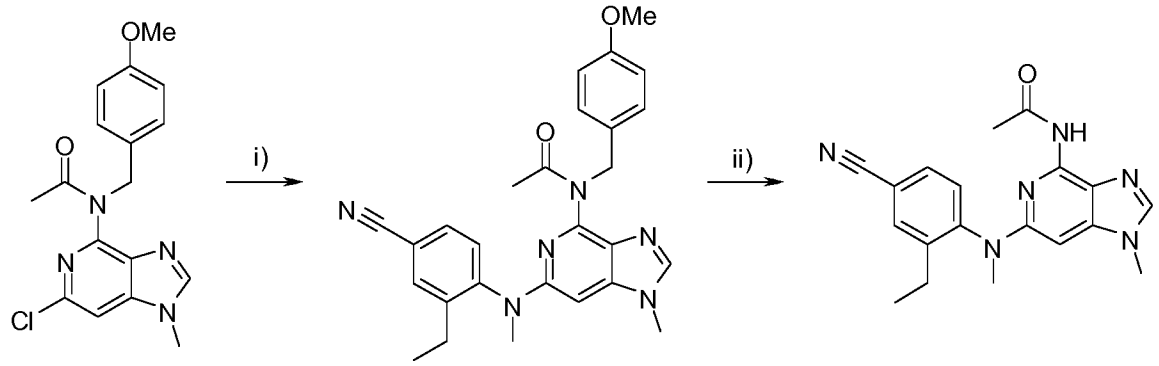
[0312] Prepared by method B using compound 105 (1 eq = 0.25 mmol) to give the desired compound after 4 h. The organic residue is purified by silica chromatography (MeOH/DCM; 0:100 to 5:95) to give the desired compound.

3.12.2. Step ii): Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0313] Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide (1 eq, 0.25 mmol) is dissolved in 4 mL of dry DCM. TFA (35 eq, 649 µL) is carefully added at room temperature, after which the solution is left stirring overnight. After completion of the reaction, extraction with sat. $NaHCO_3$ and DCM (3 x 30 mL) is performed. Drying over anhydrous sodium sulfate, concentration under reduced pressure and purification of the crude organic residue through silica chromatography (MeOH/EtOAc; 0:100 to 5:95) affords the desired compound.

[0314] ^{1}H NMR (300 MHz, $CHCl_3$-d) 8.43 (1 H, s), 7.60 (1 H, s), 7.40 (1 H, s), 7.29 (1 H, dd), 5.94 (1 H, s), 3.69 (3 H, s), 3.34 (3 H, s), 2.60 (2 H, q), 2.65-2.55 (1 H, m), 1.17 (3 H, t), 1.08-1.03 (2 H, m), 0.60-0.54 (2 H, m).

3.13. Compound 14: N-(6-((4-cyano-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



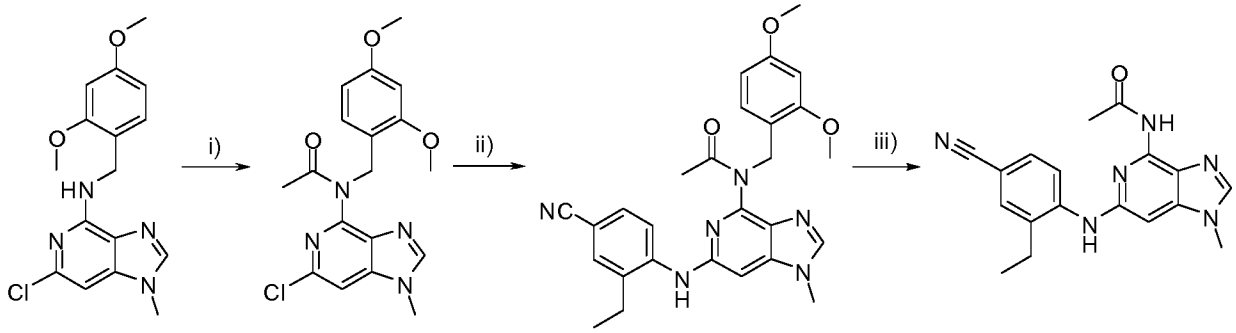
3.13.1. Step i)

[0315] Method A using compound 1 which is formed by the same synthetic route as intermediate 5.

3.13.2. Step ii):

[0316] Method D is used. the final product is isolated by preparative HPLC.

3.14. Compound 15: N-(6-(4-cyano-2-ethylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



3.14.1. Step i)

[0317] Acetyl chloride (202.6 µL, 1.953) is added to a solution of 6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxy-benzyl)-amine (intermediate 7) (500 mg, 1.502 mmol) and Pyridine (202.6 µL, 4.507) in DCM (3 mL) and the reaction mixture is stirred at room temperature overnight. The reaction mixture is diluted with water (15 mL) and extracted with DCM (3x15 mL). The combined organic extracts are dried over anhydrous Na_2SO_4 and evaporated to yield the crude product which is purified on BIOTAGE SP1 purification device, by chromatography, using 50 g normal phase silica SNAP column and DCM:MeOH solvent system (gradient 0-15% of MeOH in 15 CV) to afford the desired product.

3.14.2. Step ii)

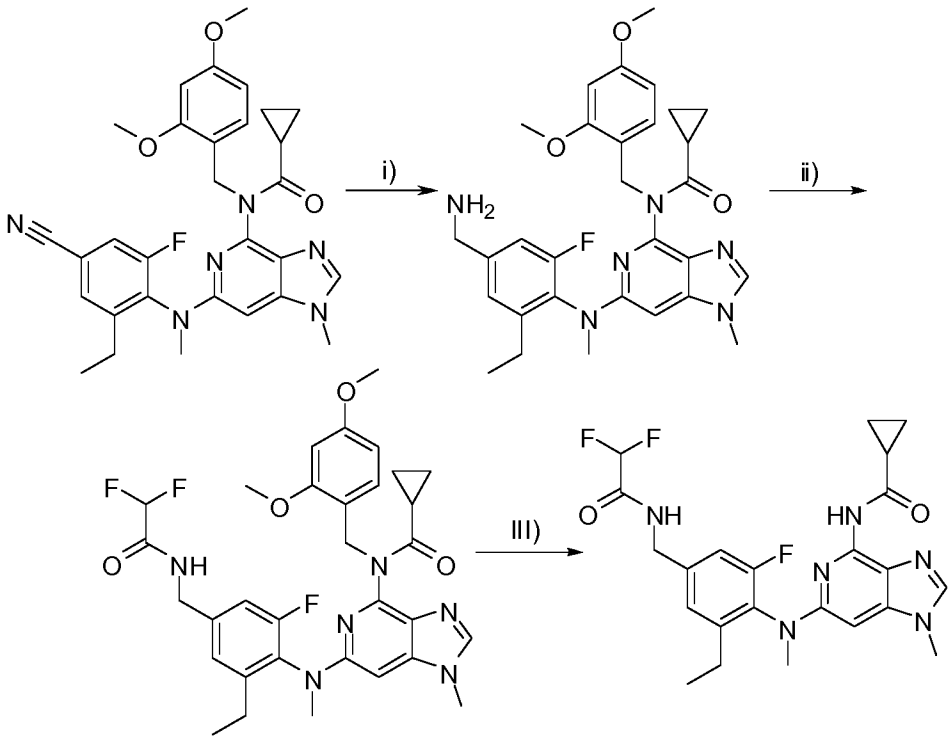
[0318] Preparation: Method A

3.14.3. Step iii)

[0319] To a solution of the compound obtained in the previous Step 49 mg, 0.101 mmol) in DCM (1 mL) is added acetic anhydride (544.7 µL, 7.070 mmol) The resulting solution is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and loaded onto an SCX column (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) in a mixture of DCM and MeOH. MeOH (15 mL) is passed through the column and the compound is eluted with 7N NH3 in MeOH : MeOH = 1:4 (15 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0320] LC-MS, m/z = 335.15 $[M+H]^+$

3.15. Compound 16: N-(6-((4-((2,2-difluoroacetamido)methyl)-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.15.1. Step i)

[0321] $NiCl_2.6H_2O$ (116.8 mg, 0.492 mmol) and TFA (291.6 µL, 3.785 mmol) are added to a solution of cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (prepared by method A and B using intermediate 23 and 8) (266.7 mg, 0.492 mmol) in MeOH (5.50 mL) at 0 °C. $NaBH_4$ (148.7 mg, 3.932 mmol) is added slowly and the mixture is allowed to warm up to room temperature. After 2.5 h, sat $NaHCO_3$ (25 mL) and EtOAc (15 mL) are added to the reaction mixture. The aqueous layer is extracted with EtOAc (2 × 15 mL), and the combined organics are dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product which is used in the next step without further purification.

[0322] LC-MS: m/z = 547.31 $[M+H]^+$.

3.15.2. Step ii)

[0323] Difluoroacetic anhydride (13.71 µL, 0.110 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(4-aminomethyl-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (60.3 mg, 0.110 mmol) in dry DCM (1.20 mL) and the reaction mixture stirred at room temperature for 1 h. The reaction mixture is then loaded onto a SaX column (200 mg, 0.36 mmol (nominal), preconditioned with 10 mL of MeOH). MeOH (25 mL) is passed through the column and the filtrate is concentrated *in vacuo* to give the desired product.

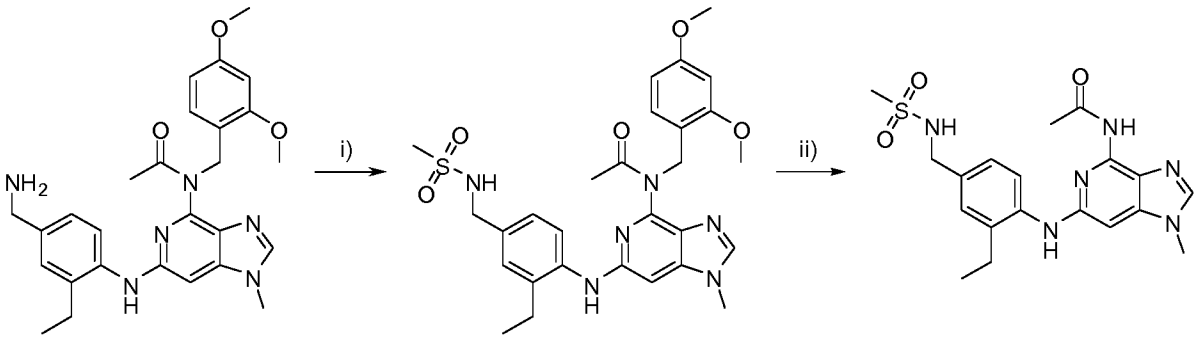
3.15.3. Step iii)

[0324] TFA (191.7 µL, 2.488 mmol) is added to a solution of cyclopropanecarboxylic acid [6-({4-[(2,2-difluoro-acetylamino)-methyl]-2-ethyl-6-fluoro-phenyl}-methyl-amino)-1-methyl-1H-imidazo [4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide (50.0 mg, 0.071 mmol) in DCM (0.93 mL) and the solution stirred at room temperature for 2.5 h. The reaction mixture is loaded onto an SCX column (400 mg, 3.0 mmol/g, preconditioned with 25 mL of MeOH). MeOH (25 mL) is passed through the column and the compound eluted with 7N NH_3 in MeOH : MeOH = 1:4 (25 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0325] ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm: 0.49 – 0.66 (m, 2H), 0.66 – 0.80 (m, 2H), 1.08 (t, 3H), 2.19 – 2.35 (m, 1H), 3.25 (s, 3H), 3.64 (s, 3H), 4.29 – 4.45 (m, 2H), 6.14 (s, 1H), 6.32 (t, 1H), 7.03 (d, 1H), 7.09 (s, 1H), 7.94 (s, 1H), 9.37 (s, 1H), 9.55 (s, 1H).

[0326] LC-MS:, m/z = 475.09 $[M+H]^+$.

3.16. Compound 17: N-(6-(2-ethyl-4-(methylsulfonamidomethyl)phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



3.16.1. Step i)

[0327] Methane sulfonylchloride (14.4 µL, 0.186) is added to a solution of N-[6-(4-Aminomethyl-2-ethyl-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-N-(2,4-dimethoxy-benzyl)-acetamide (synthesis described above) (70 mg, 0.143 mmol) and pyridine (34.5 µL, 0.429 mmol) in DCM (2 mL) and the reaction is stirred at room temperature overnight. After 16h, additional pyridine (17.3 µL, 0.215 mmol) is added and the reaction is stirred at room temperature overnight. The reaction mixture is concentrated *in vacuo*. The sample is diluated with water (30 mL) and extracted with DCM (3x30 mL). The combined organic extracts are dried over anhydrous Na_2SO_4 and evaporated to yield the crude product. The sample is purified on BIOTAGE SP1 purification device, by chromatography, using 10 g

normal phase silica SNAP column and DCM:MeOH solvent system (gradient 0-10% of MeOH in 15 CV). Solvent from gathered fractions of appropriate composition is evaporated. The desired product is isolated.

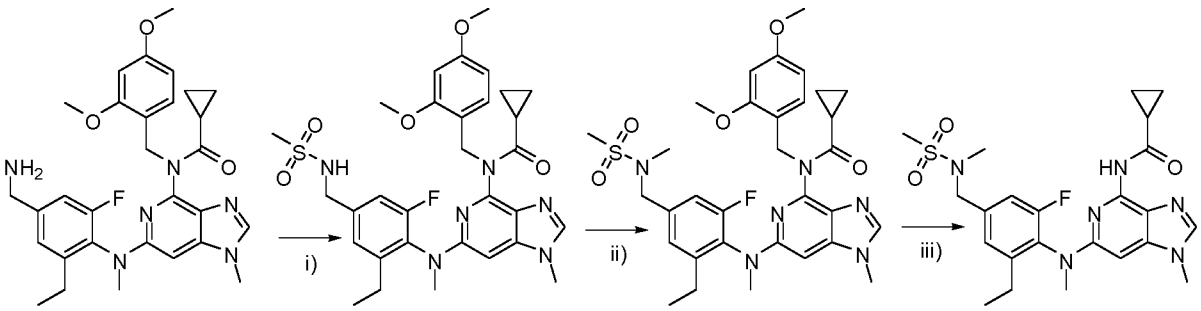
3.16.2. Step ii)

[0328] To a solution of N-(2,4-Dimethoxy-benzyl)-N-{6-[2-ethyl-4-(methanesulfonylamino-methyl)-phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-acetamide (28.5 mg, 0.050 mmol) in DCM (1 mL) is added TFA (193 µL, 2.500 mmol) The resulting solution is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and loaded onto an SCX column (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) in a mixture of DCM and MeOH. MeOH (15 mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (15 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0329] ^{1}H NMR (DMSO-d_6) : 9.78 (br. s., 1H), 7.97 (s, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 7.49 (t, 1H), 7.20 (s, 1H), 7.13 (d, 1H), 6.46 (s, 1H), 4.12 (d, 2H), 3.66 (s, 3H), 2.86 (s, 3H), 2.65 (q, 2H), 2.12 (s, 3H), 1.14 (t, 3H)

[0330] LC-MS m/z = 417.34 $[M+H]^+$

3.17. Compound 18: N-(6-((2-ethyl-6-fluoro-4-((N-methylmethylsulfonamido)methyl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.17.1. Step i)

[0331] Pyridine (44.4 µL, 0.549 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(4-aminomethyl-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (synthesis decribed above) (100.0 mg, 0.183 mmol) and methanesulfonyl chloride (15.6 µL,0.201 mmol) in dry DCM (1.70 mL) and the reaction mixture stirred at room temperature overnight. To the reaction mixture methanesulfonyl chloride (15.6 µL, 0.201 mmol) and pyridine (44.4 µL, 0.549 mmol) are added. Stirring is continued at room temperature overnight. To the reaction mixture, water (15 mL) is then added and extracted with DCM (3 × 10 mL). The combined organic layers are washed with sat $NaHCO_3$ (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the desired product.

3.17.2. Step ii)

[0332] NaH (60% dispersion in mineral oil, 2.0 mg, 0.050 mmol) is added to a solution of cyclopropane carboxylic acid (2,4-dimethoxy-benzyl)-(6-{[2-ethyl-6-fluoro-4-(methanesulfonylamino-methyl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide (28.4 mg, 0.045 mmol) in dry DMF

(0.98 mL) at 0 °C. After 30 min stirring at 0 °C, iodomethane (3.13 µL, 0.050 mmol) is added and the solution stirred at room temperature for 2 h. To the reaction mixture additional NaH (60% dispersion in mineral oil, 0.2 mg, 0.005 mmol) and iodomethane (0.31 µL, 0.005 mmol) are added. Stirring is continued at room temperature overnight. To the reaction mixture water (15 mL) is added and the aqueous extracted with DCM (3 × 10 mL). Combined organic layers are dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product.

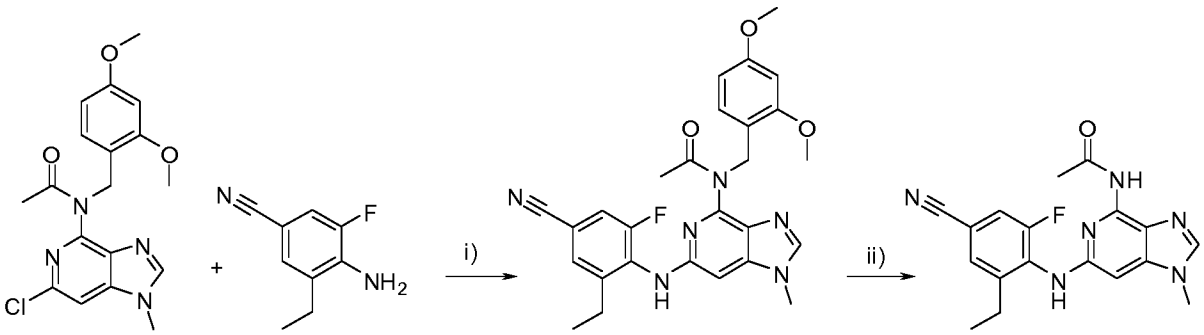
3.17.3. Step iii)

[0333] TFA (119.9 µL, 1.556 mmol) is added to a solution of cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-[6-({2-ethyl-6-fluoro-4-[(methanesulfonyl-methyl-amino)-methyl]-phenyl}-methyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-amide (28.4 mg, 0.044 mmol) in DCM (0.57 mL) and the solution stirred at room temperature overnight. The reaction mixture is loaded onto an SCX column (500 mg, >2.5 mmol/g, preconditioned with 10 mL of MeOH). MeOH (25 mL) is passed through the column and the compound eluted with 7N NH_3 in MeOH : MeOH = 1:4 (25 mL). The filtrate is concentrated *in vacuo* to give desired product.

[0334] ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 0.55 – 0.64 (m, 2H), 0.71 – 0.79 (m, 2H), 1.09 (t, 3H), 2.24 – 2.34 (m, 1H), 2.45 – 2.54 (m, 2H), 2.74 (s, 3H), 2.98 (s, 3H), 3.27 (s, 3H), 3.66 (s, 3H), 4.25 (s, 2H), 6.17 (s, 1H), 7.05 – 7.12 (m, 1H), 7.14 (s, 1H), 8.02 (s, 1H), 9.70 (s, 1H).

[0335] LC-MS m/z = 489.14 $[M+H]^+$

3.18. Compound 19: N-(6-(4-cyano-2-ethyl-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



3.18.1. Step i)

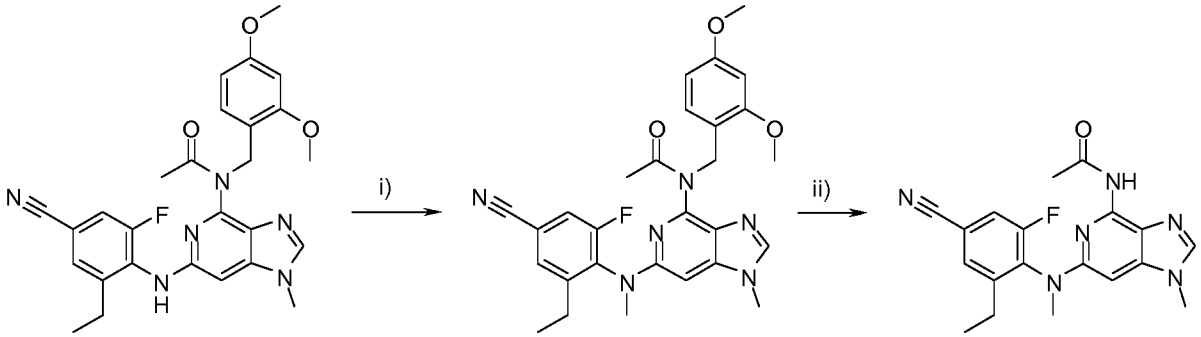
[0336] Method A: intermediates used described above.

3.18.2. Step ii)

[0337] To a solution of N-[6-(4-Cyano-2-ethyl-6-fluoro-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-N-(2,4-dimethoxy-benzyl)-acetamide (27.6 mg, 0.055 mmol) in DCM (1 mL) is added TFA (381 µL, 4.950 mmol) The resulting solution is stirred at room temperature for 5 h. The mixture is then concentrated *in vacuo* and loaded onto an SCX column (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) in a mixture of DCM and MeOH. MeOH (15 mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (15 mL). The filtrate is concentrated *in vacuo* to give the desired product.

[0338] ^{1}H NMR (DMSO-d_6) : 9.77 (br. s., 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.58 (d, 1H), 7.48 (t, 1H), 7.19 (d, 1H), 7.12 (dd, 1H), 6.45 (s, 1H), 4.11 (d, 2H), 3.62-3.67 (m, 3H), 2.85 (s, 3H), 2.64 (q, 2H), 2.11 (s, 3H), 1.13 (t, 3H)

3.19. Compound 20: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



3.19.1. Step i):

[0339] To a solution of N-[6-(4-Cyano-2-ethyl-6-fluoro-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-N-(2,4-dimethoxy-benzyl)-acetamide (43.6 mg, 0.087 mmol) in dry DMF (1 mL) cooled at 0°C is added NaH, 60% disperse in mineral oil (6.9 mg, 0.174 mmol) The resulting solution is stirred for 30 min. Then methyl iodide (7.1 µL, 0.113 mmol) is added and the mixture is stirred for 1 h. The reaction mixture is quenched with 10 mL water and extracted with DCM (3 x 10 mL). The combined organic extracts are dried over anhydrous Na_2SO_4 and evaporated to yield the crude product.

[0340] LC-MS m/z = 517.30 $[M+H]^+$

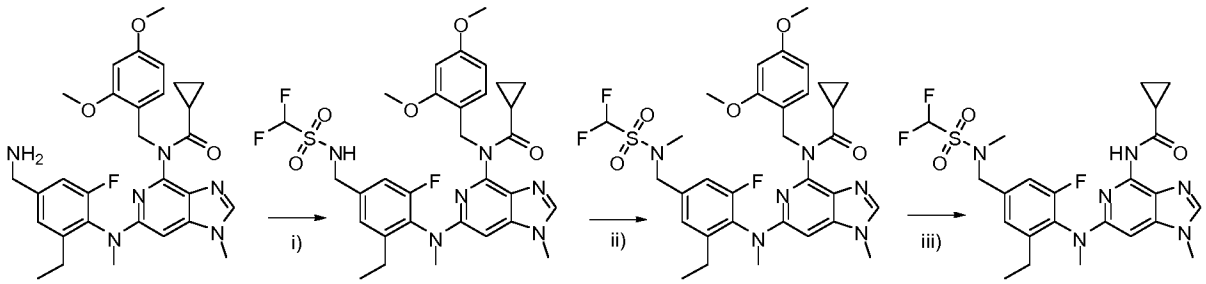
3.19.2. Step ii)

[0341] To a solution of the product obtained in step i) above (27.6 mg, 0.055 mmol) in DCM (1 mL) is added TFA (254 µL, 3.295 mmol) The resulting solution is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and loaded onto an SCX column (400 mg, 0.6 mmol/g, preconditioned with 25 mL of MeOH) in a mixture of DCM and MeOH. MeOH (15 mL) is passed through the column and the compound is eluted with 7N NH_3 in MeOH : MeOH = 1:4 (15 mL). The filtrate is concentrated *in vacuo* to give the crude product. The sample is purified again on 5 g silica gel column on SolidPrep purification system in DCM : MeOH = 20:1 solvent system (isocratic). After evaporation of solvent the desired product is isolated

[0342] ^{1}H NMR (DMSO-d_6) : 9.45 (br. s., 1H), 7.97 (s, 1H), 7.78 (d, 1H), 7.72 (s, 1H), 6.39 (br. s., 1H), 3.70 (s, 3H), 3.27 (s, 3H), 2.52 (d, 2H), 1.09 (t, 3H)

[0343] LC-MS m/z = 367.79 $[M+H]^+$

3.20. Compound 21: N-(6-((4-((1,1-difluoro-N-methylmethylsulfonamido)methyl)-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.20.1. Step i)

[0344] Pyridine (45.1 µL, 0.557 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(4-aminomethyl-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (synthesis described above)(101.5 mg, 0.186 mmol) and difluoromethanesulfonyl chloride (18.12 µL, 0.204 mmol) in dry DCM (1.70 mL) and the reaction mixture stirred at room temperature overnight. To the reaction mixture methanesulfonyl chloride (18.12 µL, 0.204 mmol) and pyridine (45.1 µL, 0.557 mmol) are added. Stirring is continued at room temperature overnight. To the reaction mixture water (15 mL) is added and extracted with DCM (3 × 10 mL). The combined organic layers are washed with sat $NaHCO_3$ (2 × 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product.

3.20.2. Step ii)

[0345] NaH (60% dispersion in mineral oil, 4.05 mg, 0.101 mmol) is added to a solution of cyclopropanecarboxylic acid [6-({4-[(difluoro-methanesulfonylamino)-methyl]-2-ethyl-6-fluoro-phenyl}-methyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide (60.8 mg, 0.092 mmol) in dry DMF (2.0 mL) at 0 °C. After 30 min stirring at 0 °C, iodomethane (6.33 µL, 0.101 mmol) is added and the solution stirred at room temperature overnight. To the reaction mixture additional NaH (60% dispersion in mineral oil, 0.4 mg, 0.010 mmol) and iodomethane (0.63 µL, 0.010 mmol) are added. Stirring is continued at room temperature for 1 h. After this time, to the reaction mixture water (15 mL) is added and the aqueous extracted with DCM (3 × 10 mL). Combined organic layers are dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product.

3.20.3. Step iii)

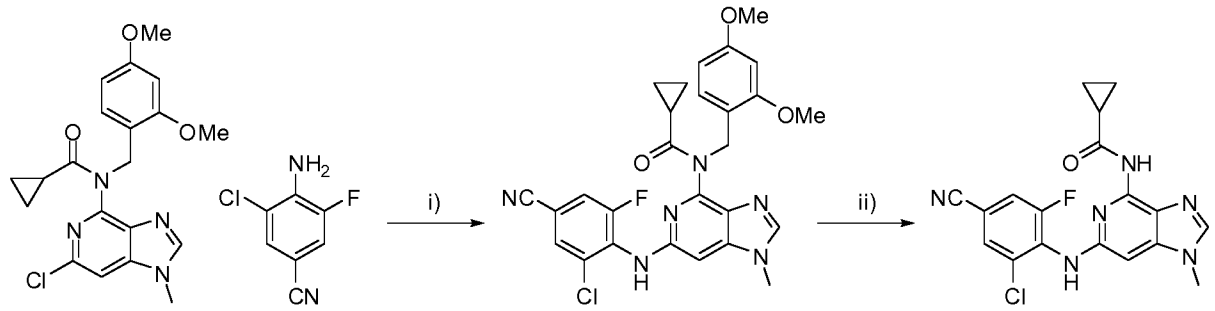
[0346] TFA (181.4 µL, 2.355 mmol) is added to a solution of cyclopropanecarboxylic acid {6-[(4-{[(difluoro-methanesulfonyl)-methyl-amino]-methyl}-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide (45.4 mg, 0.067 mmol) in DCM (0.87 mL) and the solution stirred at room temperature overnight. The reaction mixture is loaded onto an SCX column (500 mg, >2.5 mmol/g, preconditioned with 10 mL of MeOH). MeOH (25 mL) is passed through the column and the compound eluted with 7N NH_3 in MeOH : MeOH = 1:4 (25 mL). The filtrate

is concentrated *in vacuo* to give the crude product.The sample is loaded and purified on silica column (2 g). The appropriate fractions have been collected, the solvent removed to yield the desired product.

[0347] ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 0.50 – 0.66 (m, 2H), 0.69 – 0.81 (m, 2H), 1.09 (t, 3H), 2.23 – 2.34 (m, 1H), 2.45 – 2.55 (m, 2H), 2.92 (s, 3H), 3.26 (s, 3H), 3.65 (s, 3H), 4.49 (s, 2H), 6.18 (s, 1H), 7.06 – 7.13 (m, 1H), 7.24 (t, 1H), 7.98 (s, 1H), 9.63 (s, 1H).

[0348] LC-MS m/z = 525.04 $[M+H]^+$.

3.21. Compound 22: Cyclopropanecarboxylic acid [6-(2-chloro-4-cyano-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide



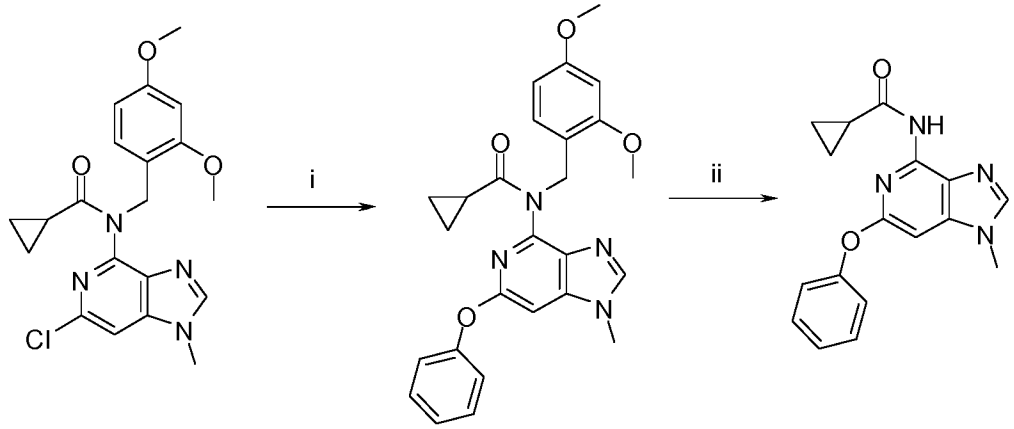
3.22. Step i): Cyclopropanecarboxylic acid [6-(2-chloro-4-cyano-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxybenzyl)amide

[0349] Prepared using Method A (1 eq = 0.75 mmol) to give the desired compound after overnight reaction. The organic residue is purified by preparative HPLC, delivering the envisaged compound.

3.22.1. Step ii): Cyclopropanecarboxylic acid [6-(2-chloro-4-cyano-6-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

[0350] To a solution of 1 eq cyclopropanecarboxylic acid [6-(2-chloro-4-cyano-6-fluorophenyl amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxybenzyl)amide (120 mg) in 25 mL of dry DCM is carefully added TFA (5 mL) at room temperature, after which the solution is left stirring overnight. After completion of the reaction as shown by LC-MS, an aq. extraction with sat. $NaHCO_3$ and DCM (3 x 30 mL) is performed. Drying over Na_2SO_4 and concentration *in vacuo*, followed by purification through preparative HPLC to afford the desired product.

3.23. Compound 23: N-(1-methyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-4-yl) cyclopropanecarboxamide



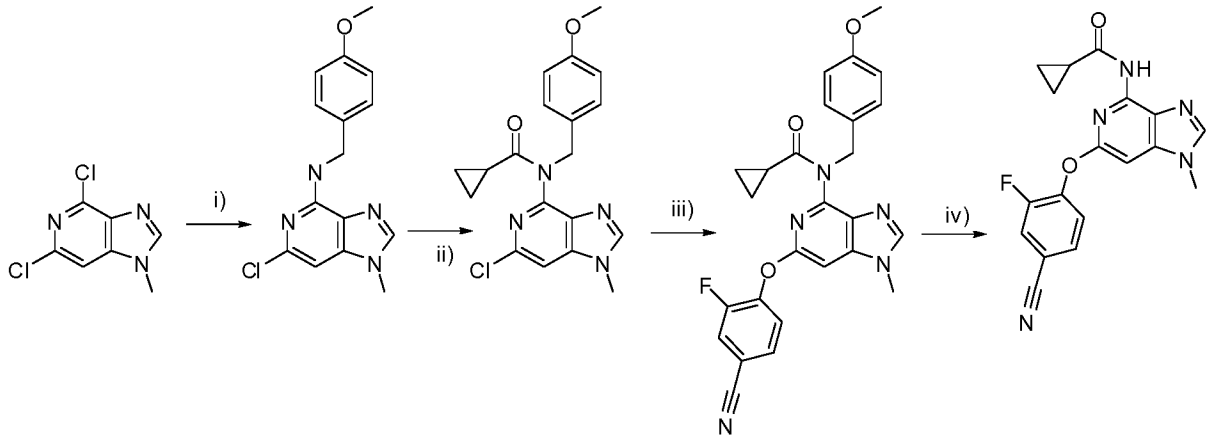
3.23.1. Step i: Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(1-methyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0351] A degassed solution of Cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxy-benzyl)-amide (1 eq, 50 mg), phenol (1.2 eq, 15 mg), CuI (0.1 eq, 3 mg), 1,10-phenantroline (0.2 eq, 5 mg) and Cs_2CO_3 (3 eq, 125 mg) in 625 µL dioxane is heated to 100°C. After 24h the temperature is increased to 150°C. After 2 days the mixture is concentrated and the residue is diluted with DCM and water. The organic layer is separated and concentrated to give a crude product that is used in the next step without purification.

3.23.2. Step ii: N-(1-methyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropane carboxamide

[0352] Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(1-methyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-4-yl)-amide from the previous step is stirred in 1:1 DCM/TFA for 1.5 h. The mixture is concentrated and the residue is dissolved in DCM and washed with sat. $NaHCO_3$. The organic layer is dried (phase separator) and concentrated. The residue is purified by preparatory HPLC to afford the desired product.

3.24. Compound 24: N-(6-(4-cyano-2-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl) cyclopropanecarboxamide



3.24.1. Step i: (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amine

[0353] A solution of 4,6-Dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (1 eq, 5 g) in 4-methoxybenzylamine (23 mL) and EtOH (35 mL) is heated to reflux. After 3 days the solid is filtered off. Trituration with MeOH gave the desired product.

3.24.2. Step ii: Cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide

[0354] Cyclopropanecarbonyl chloride (1.5 eq, 2.25 mL) is added dropwise over 15 min to an ice-cooled solution of amine (1 eq, 5.0g) in pyridine (25 mL) and DCM (41 mL). After 24h the reaction is concentrated and the obtained solid is further dried on a freeze-dryer for 5h to obtain the desired product.

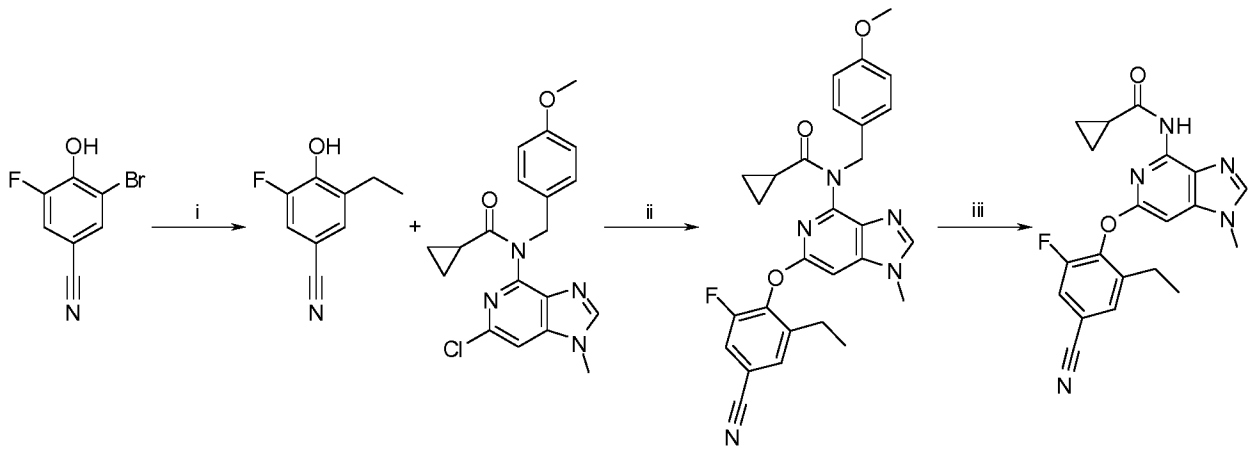
3.24.3. Step iii: Cyclopropanecarboxylic acid [6-(4-cyano-2-fluoro-phenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0355] A degassed solution of Cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide (1 eq, 47 mg), 3-Fluoro-4-hydroxy-benzonitrile (1.2 eq, 35 mg), CuI (0.05 eq, 2 mg), picolinic acid (0.1 eq, 3 mg) and K_3PO_4 (2 eq, 153 mg) in 250 µL DMSO is heated to 100°C. After 24 h the temperature is increased to 150°C. After 3 days the mixture is concentrated and the residue is diluted with DCM and water. The organic layer is separated and concentrated to give a crude product that is used in the next step without purification.

3.24.4. Step iv: N-(6-(4-cyano-2-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl) cyclopropanecarboxamide

[0356] Cyclopropanecarboxylic acid [6-(4-cyano-2-fluoro-phenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide from the previous step is stirred in 1:1 DCM/TFA (1 mL) for 16 h at 60°C. The mixture is concentrated and the residue is dissolved in DCM and washed with sat. $NaHCO_3$. The organic layer is dried (phase separator) and concentrated. The residue is purified by preparatory HPLC to afford the desired product.

Compound 25: N-(6-(4-cyano-2-ethyl-6-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl) cyclopropanecarboxamide



3.24.5. Step i: 3-Ethyl-5-fluoro-4-hydroxy-benzonitrile

[0357] To a degassed solution of 3-bromo-5fluoro-4-hydroxybenzonitrile (1 eq, 2.0 g), $PdCl_2$(dppf).DCM (0.02 eq, 152 mg) and Cs_2CO_3 (2 eq, 6.03g) in THF (18.5 mL) is added triethylborane (1M in hexane, 2 eq, 18.5 mL) and the mixture is heated to reflux. After 5 h, BEt_3 (20 mL, 1M in hexane) is added. After 2 days the mixture is concentrated and the residue is purified by silica chromatography (10-100% EtOAc in petroleum ether and flushed with MeOH) to obtain the desired product.

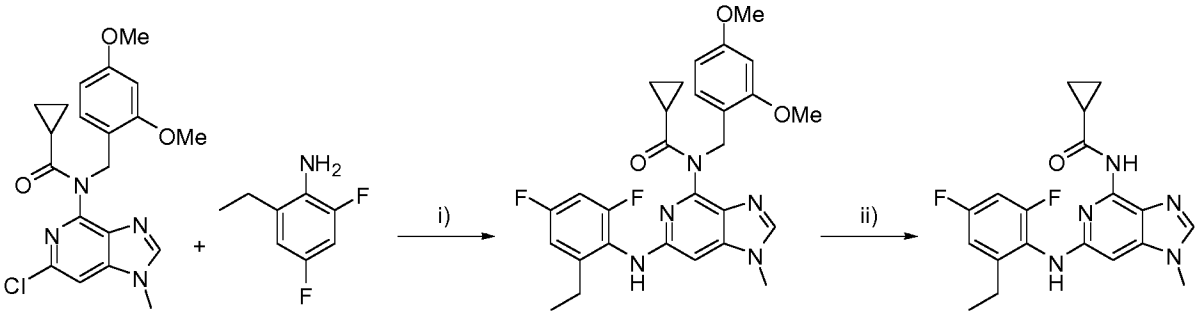
3.24.6. Step ii: Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0358] Synthesized following the same conditions used for compound 24.

3.24.7. Step iii: Cyclopropanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0359] Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(1-methyl-6-phenoxy-1H-imidazo[4,5-c]pyridin-4-yl)-amide from the previous step is stirred in 1:2 DCM/TFA (9 mL) for 16 h at 80 °C. The mixture is concentrated and the residue is dissolved in DCM and washed with sat. $NaHCO_3$. The organic layer is dried (phase separator) and concentrated. The residue is purified by preparatory HPLC to afford the desired product.

3.25. Compound 26: Cyclopropanecarboxylic acid [6-(2-ethyl-4,6-difluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide



3.25.1. Step i): Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-[6-(2-ethyl-4,6-difluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

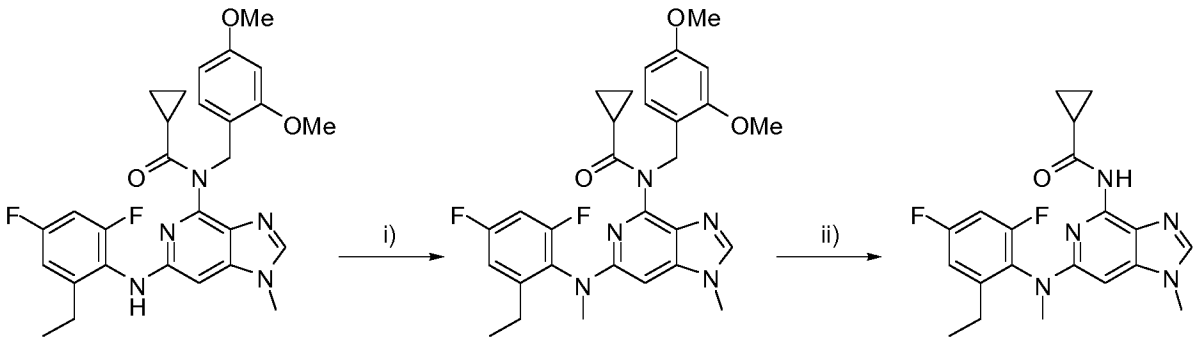
[0360] Prepared through method A using intermediate 5 (1.1 eq, 216 mg) with Intermediate 26 to give the desired compound after 1 h. The organic residue is purified by silica chromatography (petroleum ether/EtOAc; 10:90 to 0:100) to give the desired compound.

3.25.2. Step ii): Cyclopropanecarboxylic acid [6-(2-ethyl-4,6-difluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

[0361] Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-[6-(2-ethyl-4,6-difluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide (1 eq, 350 mg) is dissolved in anhydrous DCM (5 mL). TFA (1 mL) is carefully added at room temperature, after which the solution is vigorously stirred for 1 h. Upon completion, the reaction mixture is diluted with sat. $NaHCO_3$ and DCM. Aq. extraction with DCM (3 x 30 mL) is performed. The combined organics are dried over sodium sulfate and concentrated under reduced pressure. Trituration of the obtained residue in DCM yielded cyclopropanecarboxylic acid [6-(2-ethyl-4,6-difluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide.

[0362] ^1H NMR (300 MHz, DMSO-d_6) 9.82 (1 H, s), 7.92 (1 H, s), 7.84 (1 H, s), 7.12 (1 H, td), 7.02 (1 H, m), 6.13 (1 H, s), 3.64 (3 H, s), 2.60 (2 H, q), 2.20 (1 H, br. s), 1.08 (3 H, t), 0.78-0.74 (2 H, m), 0.69-0.64 (2 H, m).

3.26. Compound 27: Cyclopropanecarboxylic acid {6-[(2-ethyl-4,6-difluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



3.26.1. Step i): Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-{6-[(2-ethyl-4,6-difluorophenyl)methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

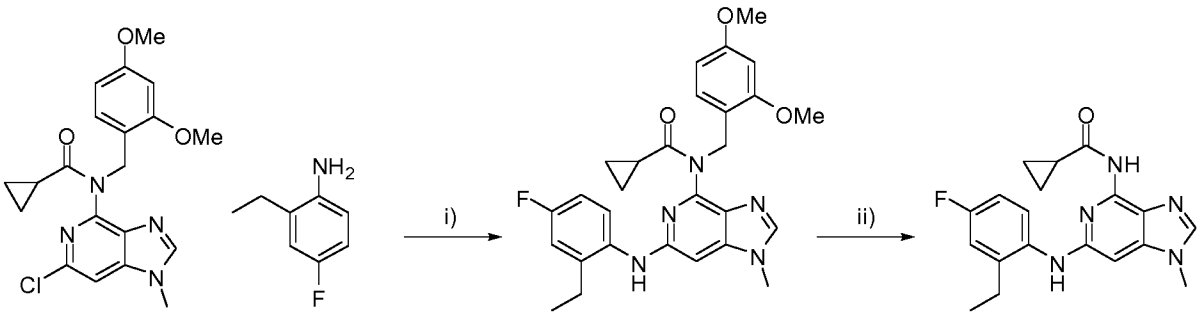
[0363] Prepared using method B (1 eq = 0.40 mmol) to give the desired compound after 1 h. The organic residue is used as such in the following deprotection step.

3.26.2. Step ii): Cyclopropanecarboxylic acid {6-[(2-ethyl-4,6-difluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0364] Crude cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-{6-[(2-ethyl-4,6-difluorophenyl) methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide (1 eq, 0.40 mmol) is dissolved in dry DCM (5 mL), TFA (1 mL) is then carefully added at room temperature, followed by overnight reaction of the solution at room temperature. After completion of the reaction, an extraction with sat. $NaHCO_3$ and DCM (3 x 30 mL) is performed. After drying over anhydrous sodium sulfate and concentration under reduced pressure, the crude organic residue is purified through preparative HPLC.

[0365] ^1H NMR (300 MHz, DMSO-d_6) 8.42 (1 H, s), 7.53 (1 H, s), 6.82-6.77 (1 H, m), 6.71 (1 H, m), 5.80 (1 H, s), 3.62 (3 H, s), 3.30 (3 H, s), 2.76 (1 H, br. s), 2.52 (2 H, q), 1.11 (3 H, t), 1.06-1.02 (2 H, m), 0.65-0.60 (2 H, m).

3.27. Compound 28: Cyclopropanecarboxylic acid [6-(2-ethyl-4-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide



3.27.1. Step i): Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-[6-(2-ethyl-4-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

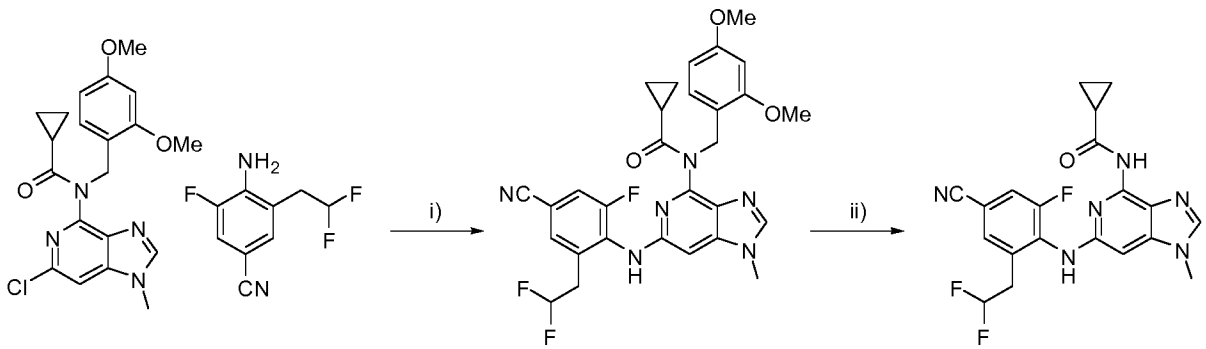
[0366] Prepared via method A using intermediate 4 (1.1 eq, 191 mg) and Intermediate 27 to give the desired compound after 1 h. The organic residue is purified by silica chromatography (MeOH/EtOAc; 0:100 to 5:95) to give the desired compound.

3.27.2. Step ii): Cyclopropanecarboxylic acid [6-(2-ethyl-4-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide

[0367] Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-[6-(2-ethyl-4-fluorophenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide (1 eq, 360 mg) is dissolved in 5 mL of anhydrous DCM. TFA (1 mL) is carefully added at room temperature, after which the solution is vigorously stirred for 2 h. LC-MS showed complete conversion into the envisaged product and the reaction mixture is diluted with sat. $NaHCO_3$ and DCM. Aq. extraction with DCM (3 x 30 mL) is performed. The combined organics are dried over sodium sulfate and concentrated under reduced pressure. Trituration of the obtained residue in DCM affords the final compound.

[0368] ^{1}H NMR (300 MHz, DMSO-d_6) 10.04 (1 H, s), 7.94 (1 H, s), 7.82 (1 H, s), 7.52 (1 H, dd), 7.06 (1 H, dd), 6.97 (1 H, td), 6.34 (1 H, s), 3.65 (3 H, s), 2.61 (2 H, q), 2.15 (1 H, br. s), 1.11 (3 H, t), 0.80-0.70 (4 H, m).

3.28. Compound 29: Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



3.28.1. Step i): Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide

[0369] Prepared using method A with 4-amino-3-(2,2-difluoroethyl)-5-fluorobenzonitrile (1.1 eq, 100 mg) and Intermediate 11 to give the desired compound after 1 h. The organic residue is purified by silica chromatography (MeOH/EtOAc; 0:100 to 10:90) to give the desired compound.

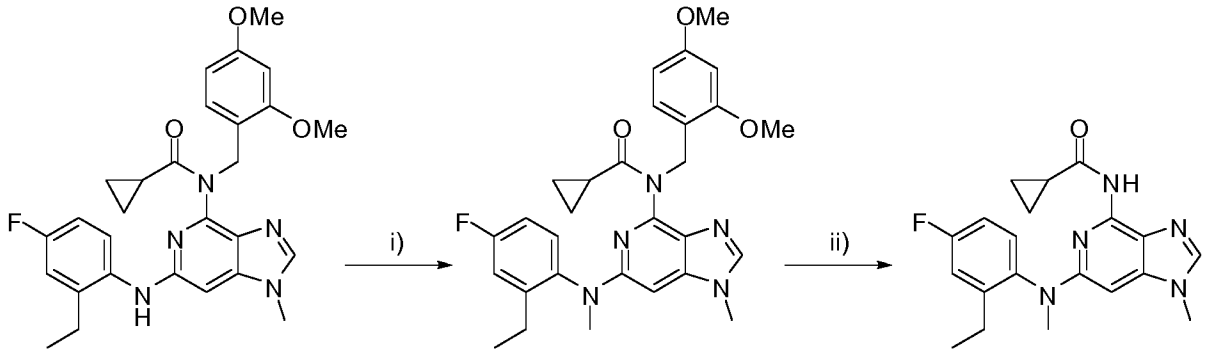
3.28.2. Step ii): Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0370] To a solution of cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide (1 eq, 152 mg) in anhydrous DCM (5 mL) is dropped carefully TFA (1 mL) at room temperature. The solution is vigorously stirred for 1 h, after which extra TFA (1 mL) is added to push the reaction towards

completion, as shown by LC-MS. The reaction mixture is diluted with sat. $NaHCO_3$ and DCM and extraction with DCM (3 x 30 mL) is performed. The combined organics are dried over anhydrous sodium sulfate and concentrated *in vacuo*, followed by purification of the crude residue through column chromatography (silica, MeOH/EtOAC; 0:100 to 10:90) to afford the desired product.

[0371] ^{1}H NMR (300 MHz, DMSO-d_6) 10.00 (1 H, s), 8.61 (1 H, s), 8.04 (1 H, s), 7.82 (1 H, dd), 7.70 (1 H, s), 6.59 (1 H, s), 6.26 (1 H, m), 3.72 (3 H, s), 3.32 (2 H, m), 2.08 (1 H, br. s), 0.76-0.72 (2 H, m), 0.70-0.64 (2 H, m).

3.29. Compound 30: Cyclopropanecarboxylic acid {6-[(2-ethyl-4-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



3.29.1. Step i): Cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-{6-[(2-ethyl-4-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

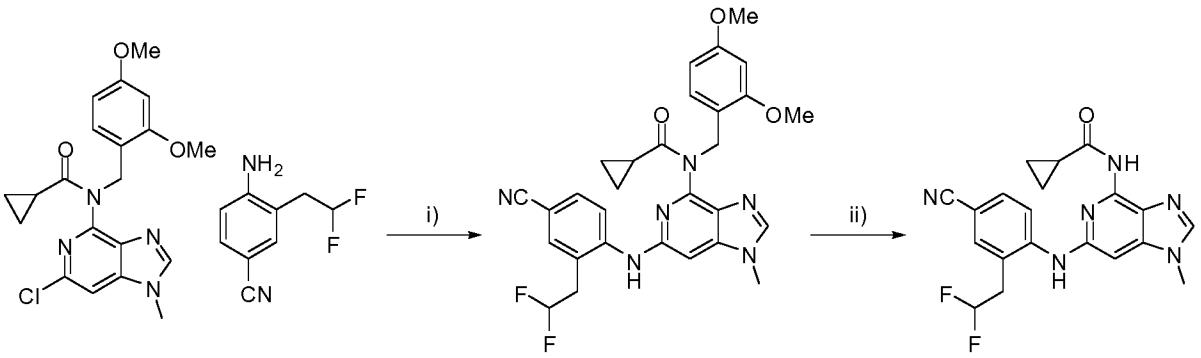
[0372] Prepared using method B (1 eq = 0.44 mmol) to give the desired compound after overnight stirring at room temperature. The organic residue, obtained after aq. work-up, is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 70:30) to give the desired compound.

3.29.2. Step ii): Cyclopropanecarboxylic acid {6-[(2-ethyl-4-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0373] To a solution of cyclopropanecarboxylic acid (2,4-dimethoxybenzyl)-{6-[(2-ethyl-4-fluorophenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide (1 eq, 155 mg) in dry DCM (5 mL) is TFA (1 mL) carefully dropped at room temperature, followed by vigorously stirring for 1 h at room temperature. After completion, the reaction mixture is extracted with sat. $NaHCO_3$ and DCM (3 x 30 mL). After drying over anhydrous sodium sulfate and concentration *in vacuo*, the wanted end product could be triturated from acetonitrile, yielding the desired product.

[0374] ^{1}H NMR (300 MHz, DMSO-d_6) 9.73 (1 H, s), 7.91 (1 H, s), 7.24-7.19 (2 H, m), 7.11 (1 H, td), 5.94 (1 H, s), 3.59 (3 H, s), 3.29 (3 H, s), 2.44 (2 H, q), 2.30 (1 H, br. s), 1.09 (3 H, t), 0.80-0.75 (2 H, m), 0.68-0.64 (2 H, m).

3.30. Compound 31: Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



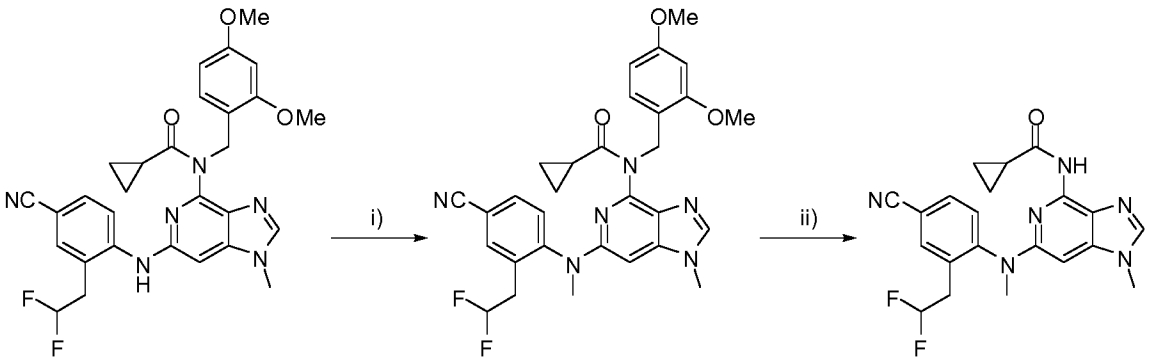
3.30.1. Step i): Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl) phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide

[0375] Prepared via method A using 4-amino-3-(2,2-difluoroethyl)benzonitrile intermediate 10 (1.1 eq, 250 mg) to give the desired compound after 1 h. The organic residue is purified by silica chromatography (MeOH/EtOAc; 0:100 to 10:90) to give the desired compound.

3.30.2. Step ii): Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl) phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0376] Cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide (1 eq, 186 mg) is dissolved in anhydrous DCM (5 mL). TFA (1 mL) is carefully added at room temperature, after which the solution is vigorously stirred for 4 h. LC-MS showed complete conversion into the envisaged product and the reaction mixture is diluted with sat. $NaHCO_3$ and DCM. Aq. extraction with DCM (3 x 30 mL) is performed. The combined organics are dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification of the crude residue through column chromatography (silica, MeOH/EtOAC; 0:100 to 10:90) yields cyclopropanecarboxylic acid {6-[4-cyano-2-(2,2-difluoroethyl)phenylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide.

3.31. Compound 32: Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)phenyl]methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)amide



3.31.1. Step i): Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)phenyl] methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amide

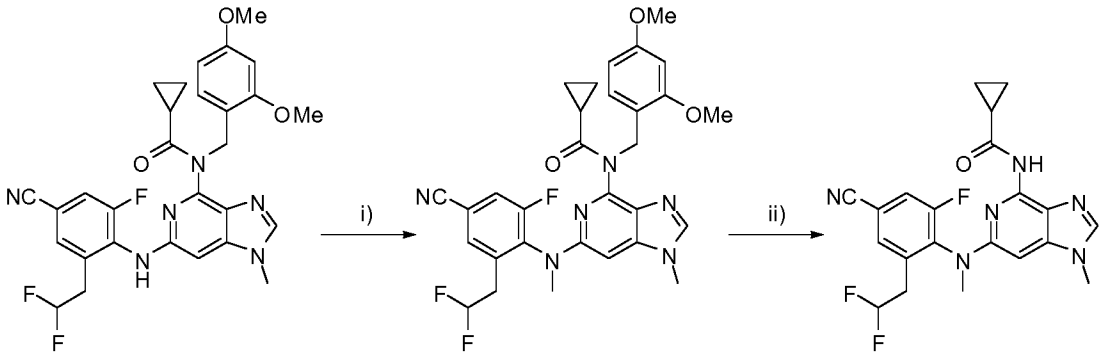
[0377] Prepared through method B (1 eq = 0.33 mmol) to give the desired compound after 5 h. The organic residue is used as such in the following deprotection step.

3.31.2. Step ii): Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl) phenyl]methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)amide

[0378] Crude cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)phenyl]methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amide (1 eq, 0.33 mmol) is dissolved in 5 mL of dry DCM, whereto TFA (1 mL) is carefully dropped at room temperature, followed by stirring at room temperature for 6 h. After completion of the reaction as shown by LC-MS, an extraction with sat. $NaHCO_3$ and DCM (3 x 30 mL) is performed. After drying over Na_2SO_4 and concentration under reduced pressure, the crude organic residue is purified through chromatography (MeOH/EtOAc; 0:100 to 10:90) affording the desired compound.

[0379] ^{1}H NMR (300 MHz, DMSO-d_6) 10.36 (1 H, s), 8.52 (1 H, s), 7.97 (1 H, s), 7.88 (1 H, d), 7.49 (1 H, d), 6.48 (1 H, s), 6.27 (1 H, m), 3.76 (3 H, s), 3.35 (3 H, s), 3.08 (2 H, m), 2.13 (1 H, br s), 0.86-0.80 (2 H, m), 0.77-0.72 (2 H, m).

Compound 33: Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenyl] methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)amide



3.31.3. Step i): Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)-6-fluoro phenyl]methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amide

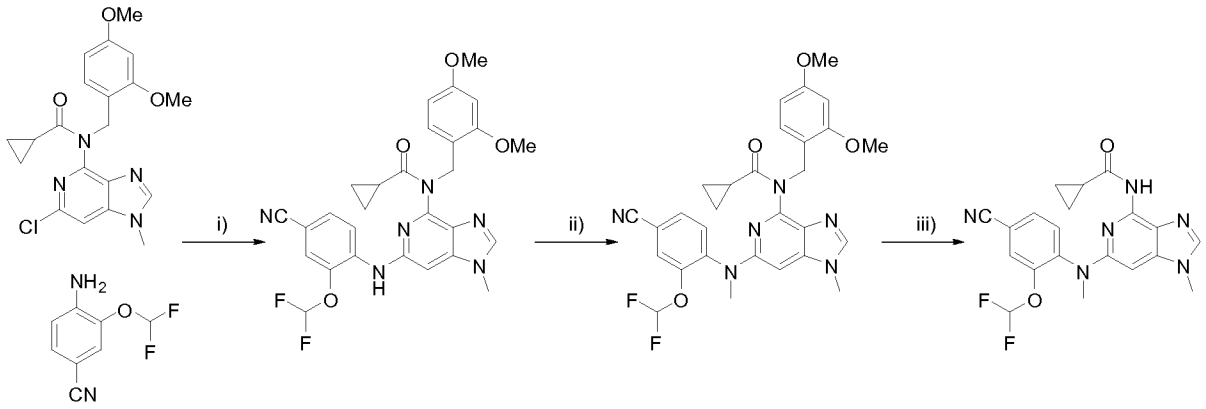
[0380] Prepared using method B (1 eq = 0.20 mmol) to give the desired compound after overnight reaction. The organic residue is purified through column chromatography (silica, MeOH/EtOAc; 0:100 to 10:90), providing the desired product.

3.31.4. Step ii): Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenyl]methylamino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)amide

[0381] Cyclopropanecarboxylic acid (6-{[4-cyano-2-(2,2-difluoroethyl)-6-fluorophenyl]methyl amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxybenzyl)amide (1 eq, 130 mg) is dissolved in dry DCM (5 mL), whereto TFA (1 mL) is carefully dropped at room temperature, followed by overnight reaction of the solution at room temperature. After completion of the reaction as shown by LC-MS, an extraction with sat. $NaHCO_3$ and DCM (3 x 30 mL) is performed. After drying over anhydrous sodium

sulfate and concentration under reduced pressure, the crude organic residue is purified through preparative HPLC to afford the desired product.

3.32. Compound 34: Cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxyphenyl) methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide



3.32.1. Step i): Cyclopropanecarboxylic acid [6-(4-cyano-2-difluoromethoxyphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxybenzyl)amide

[0382] Prepared via method A using 4-amino-3-difluoromethoxybenzonitrile (1.1 eq, 0.37 mmol) and Intermediate 28 to give the desired compound after 2 h. The organic residue is purified by silica chromatography (MeOH/EtOAc; 0:100 to 10:90) to give the desired compound.

3.32.2. Step ii): Cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxyphenyl) methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide

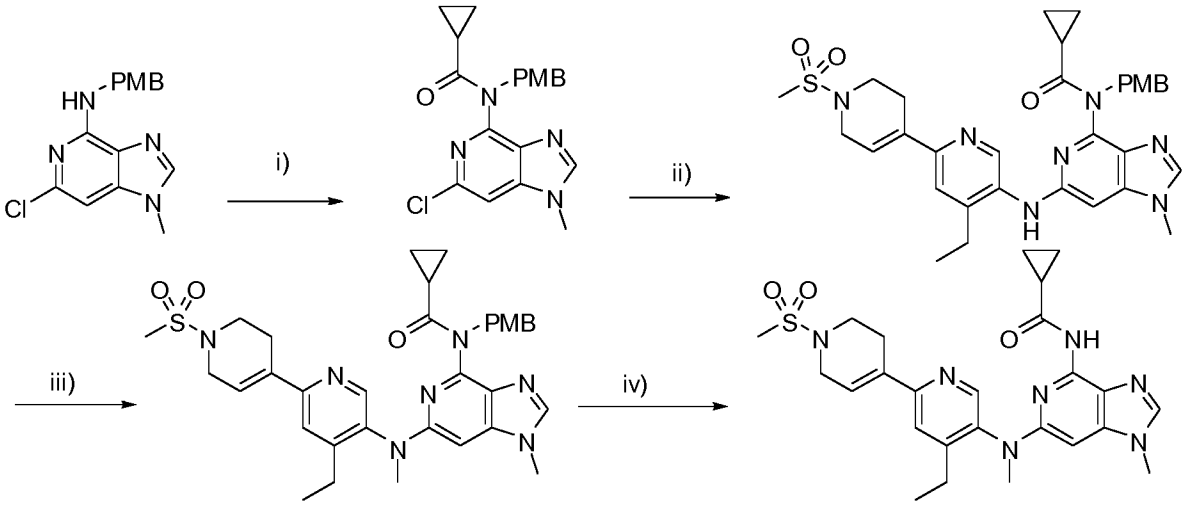
[0383] Prepared through method B (1 eq = 0.20 mmol) to give the desired compound after overnight reaction. The organic residue is purified through column chromatography (silica, MeOH/EtOAc; 0:100 to 10:90).

3.32.3. Step iii): Cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxyphenyl) methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}amide

[0384] Desired cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxyphenyl)methylamino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxybenzyl)amide (1 eq, 95 mg) is dissolved in anhydrous DCM (3 mL), whereto TFA (1 mL) is carefully dropped at room temperature. The solution is vigorously stirred for 1 h, after which extra TFA (1 mL) is added to push the reaction towards completion, as shown by LC-MS. The reaction mixture is diluted with sat. $NaHCO_3$ and DCM and extraction with DCM (3 x 30 mL) is performed. The combined organics are dried over sodium sulfate and concentrated *in vacuo*, yielding the desired product.

[0385] ^1H NMR (300 MHz, $CHCl_3$-d) 7.80 (1 H, s), 7.55-.748 (2 H, m), 7.41 (1 H, d), 6.46 (1 H, t), 6.25 (1 H, s), 3.76 (3 H, s), 3.44 (3 H, s), 2.31 (1 H, br. s), 1.05 (2 H, br. s), 0.69-0.64 (2 H, m).

3.33. Compound 35: N-(6-((4-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.33.1. Step i): Cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide

[0386] A solution of (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amine (1.0 eq, 200 mg), cyclopropanecarbonyl chloride (1.5 eq, 90 µL) and pyridine (1 mL) in dry DCM (2 mL) is heated at 50 °C. After 2 h, acid chloride (0.5 eq, 30 µL) is added and stirring at 50 °C is continued for 2 more h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The product is used in the next step without further purification.

3.33.2. Step ii): Cyclopropanecarboxylic acid [6-(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0387] A solution of cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide (1.2 eq, 245 mg), 4-Ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamine (Intermediate 29) (1.0 eq, 150 mg), Cs_2CO_3 (2.5 eq, 450 mg) in dry 1,4-dioxane (3 mL) is degassed under nitrogen flow. To this solution is added Pd_2dba_3 (0.1 eq, 55 mg) and XPhos (0.3 eq, 85 mg) and the resulting mixture is degassed again and stirred at 100°C for 3 h. The mixture is diluted with DCM, filtered through a celite pad. The filtrate is washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The residue is purified by silica chromatography (DCM/MeOH: 100/0 to 95/5) to afford the desired product.

3.33.3. Step iii): Cyclopropanecarboxylic acid {6-[(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

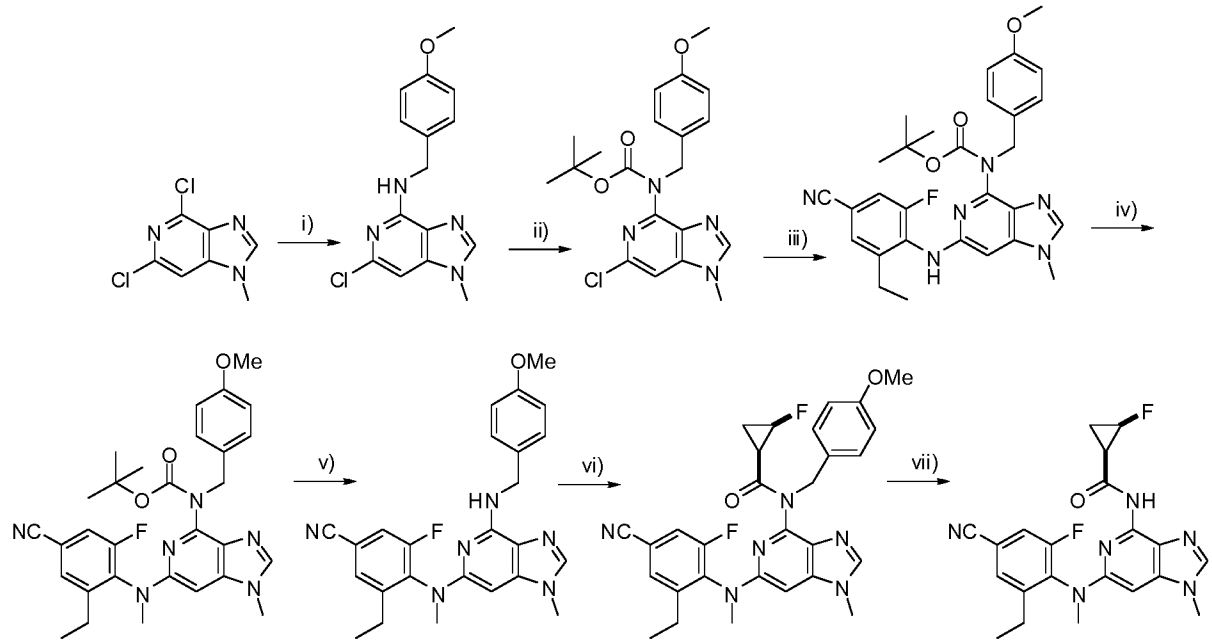
[0388] To a solution of cyclopropanecarboxylic acid [6-(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide (210 mg, 1.0 eq) and NaH (3.0 eq, 40 mg) in dry THF at 0°C is added iodomethane (3.0 eq, 55 µL)

and the mixture is stirred at room temperature for 2 h. The solution is diluted with EtOAc and water. The organic layer is washed with brine, dried (Na_2SO_4), filtered and concentrated.

3.33.4. Step iv) : N-(6-((4-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0389] Cyclopropanecarboxylic acid {6-[(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide (1.0 eq, 200 mg) is dissolved in TFA (3 mL) and the mixture is heated at 80°C for 16 h. The mixture is carefully neutralized with a saturated solution of $NaHCO_3$, and the product is extracted with DCM. The organic layer is filtered through a phase separator and concentrated. The residue is purified by silica chromatography (DCM/MeOH: 100/0 to 94/6) to afford the desired product.

3.34. Compound 36: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.34.1. Step i): (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amine

[0390] A mixture of 4,6-dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (1 eq, 2.5 g) and 4-methoxy-benzylamine (3 eq, 4.9 mL) is heated at 130 °C for 18 h then allowed to cool to room temperature, water is added and the precipitate filtered. Trituration with EtOAc and petrol ether affords the compound.

3.34.2. Step ii): (6-Chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-carbamic acid tert-butyl ester

NaHMDS (1M in THF, 1.3 eq, 0.86 mL) is added to the amine (1.0 eq, 200 mg) in THF (10 mL) at -78°C. After 30 min, di-tert-butyl dicarbonate (1.1 eq, 160 mg) is added, the reaction warmed to room temperature and stirred for 18 h. The mixture is cooled again at -78 °C, NaHMDS (1M in THF, 1.3 eq, 0.86 mL) is added followed, after 30 min, by di-tert-butyl dicarbonate (1.1 eq, 160 mg), warmed up to room temperature and stirred for 24 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$,

passed through a phase separator and concentrated to give the desired product that is used in the next step without further purification.

3.34.3. Step iii) and iv) : {6-[(4-Cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-carbamic acid tert-butyl ester

[0391] Synthesised following the same conditions used for Compound 7 (step ii and iii).

3.34.4. Step v): 3-Ethyl-5-fluoro-4-{[4-(4-methoxy-benzylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-benzonitrile

[0392] To the crude Boc-protected amine in DCM (5 mL) is added TFA (2 mL) and the reaction is stirred at room temperature for 1 h. The resulting mixture is concentrated, redissolved in DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated to give a crude mixture that is used in the next step without further purification.

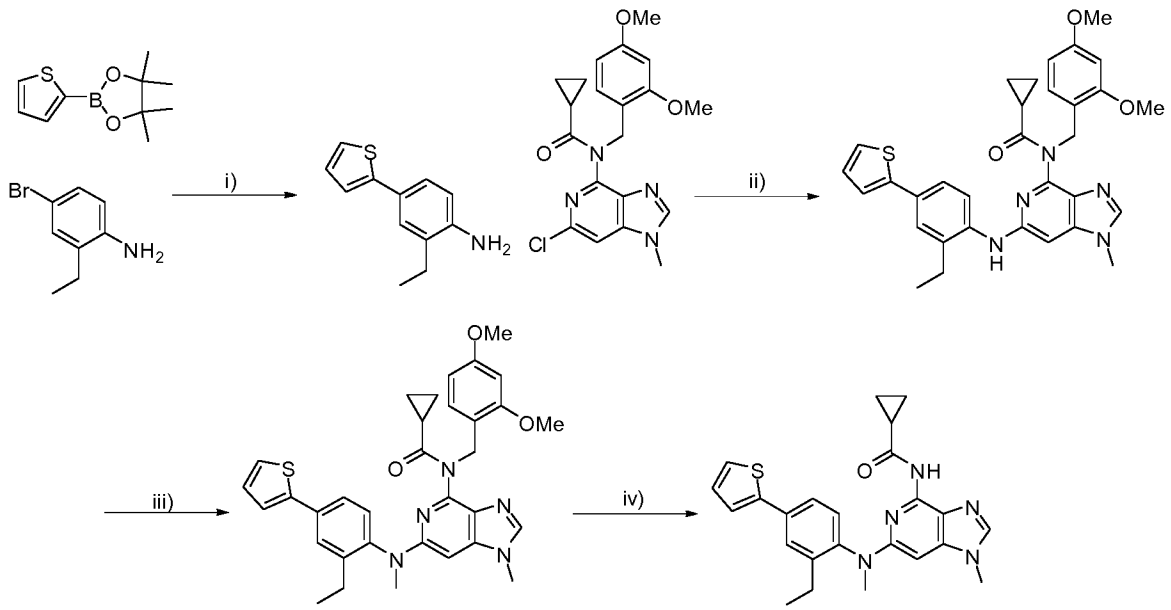
3.34.5. Step vi): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0393] To cis-2-fluoro-cyclopropanecarboxylic acid (4 eq, 142 mg) in dry DCM (2 mL) at 0 °C is added oxalyl chloride (4 eq, 115 µL) followed by 1 drop of DMF. After 10 min, the crude amine in DCM (2 mL) is added, followed by pyridine (0.5 mL), and the mixture warmed to room temperature and stirred for 18 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated. Used in the next step without further purification.

3.34.6. Step vii): N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0394] A mixture of the crude PMB-protected amine in TFA (5 mL) is heated at 100 °C. After 3 h, the solution is concentrated. Purification by preparative HPLC affords the desired product.

3.35. Compound 37: N-(6-((2-ethyl-4-(thiophen-2-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.35.1. Step i): 2-Ethyl-4-thiophen-2-yl-phenylamine

[0395] A mixture of 4-bromo-2-ethyl-phenylamine (1.0 eq, 0.71 mL), 4,4,5,5-tetramethyl-2-thiophen-2-yl -[1,3,2]dioxaborolane (1.0 eq, 1.05 g), $PdCl_2$(dppf).DCM (0.1 eq, 408 mg) and Cs_2CO_3 (3.0 eq, 409 g) in dioxane/water (4:1, 15 mL) is stirred at 85 °C. After 18 h, the resulting mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated to afford the compound that is used without further purification.

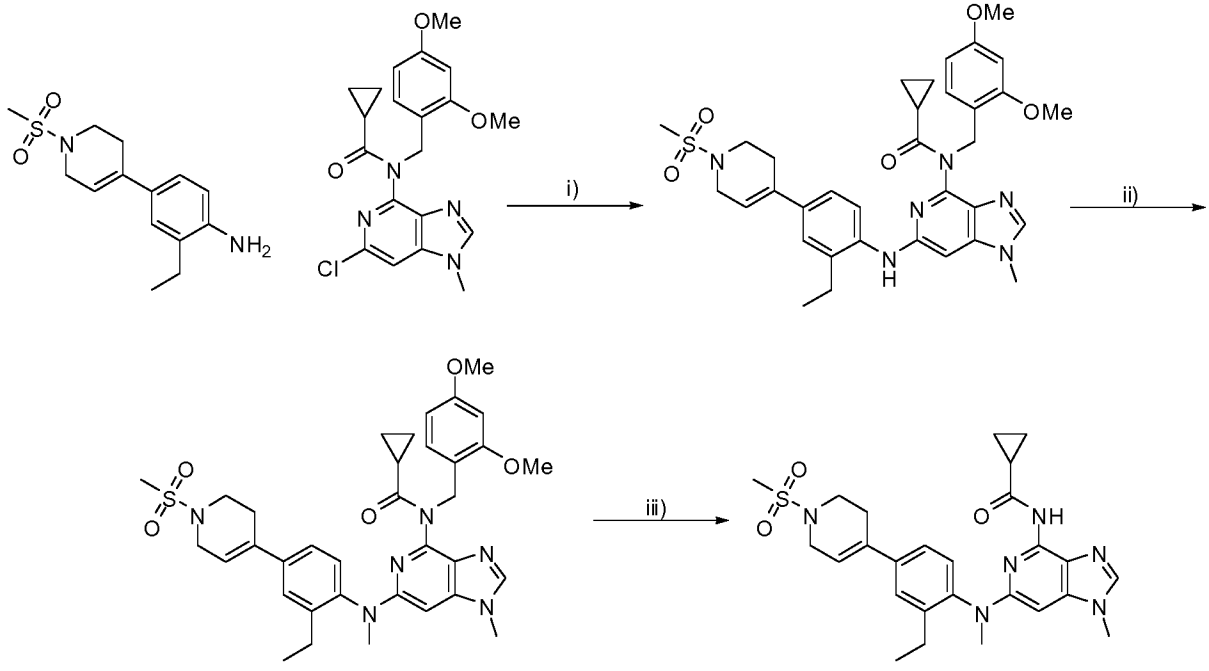
3.35.2. Step ii and iii : Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-{6-[(2-ethyl-4-thiophen-2-yl-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0396] Synthesised following the same conditions used for Compound 7 (step ii and iii).

3.35.3. Step iv : N-(6-((2-ethyl-4-(thiophen-2-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0397] TFA (1 mL) is added to the crude DMB-protected compound (0.37 mmol) in DCM (4 mL) and stirred room temperature for 2 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Silica chromatography (MeOH/DCM; 0:100 to 1.5:98.5) affords the desired compound.

3.36. Compound 38: N-(6-((2-ethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



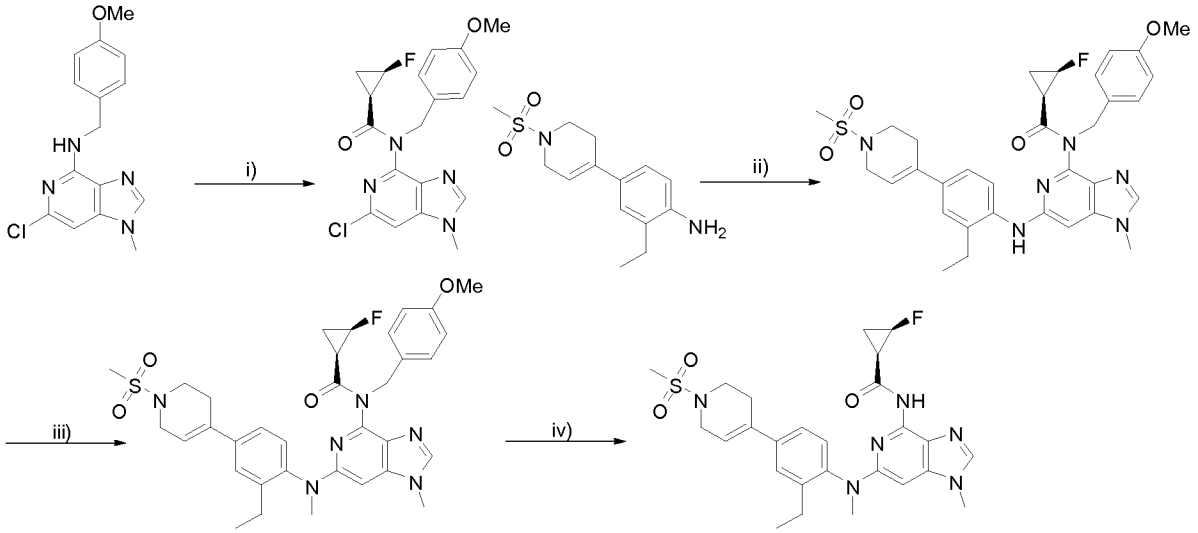
3.36.1. Step i and ii : Cyclopropanecarboxylic acid (2,4-dimethoxy-benzyl)-(6-{[2-ethyl-4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0398] Synthesised following the same conditions used for compound 7 (step ii and iii).

3.36.2. Step iii : N-(6-((2-ethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0399] Synthesised following the same conditions used for Compound 37 (step iv).

3.37. Compound 39: (1R,2R)-N-(6-((2-ethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide



3.37.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide

[0400] Synthesised following the same conditions used for compound 36 (step vi).

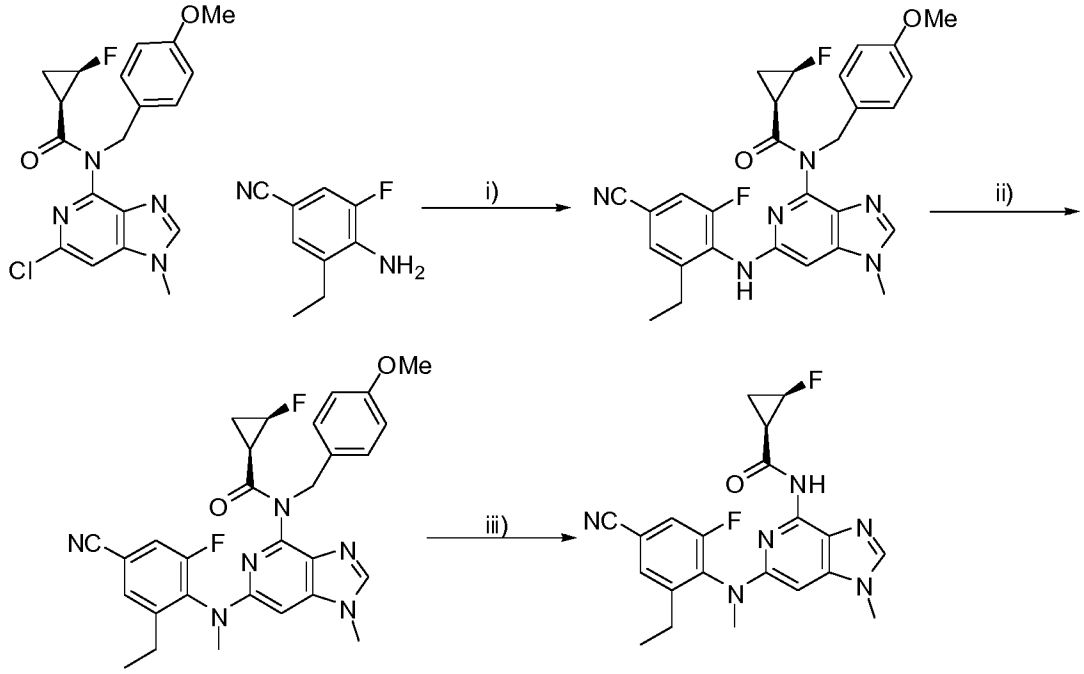
3.37.2. Step ii and iii : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[2-ethyl-4-(1-methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide

[0401] Synthesised following the same conditions used for compound 7(step ii and iii).

3.37.3. Step iv : (1R,2R)-N-(6-((2-ethyl-4-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0402] A solution of the crude PMB-protected compound (0.50 mmol) in TFA is stirred at 80 °C for 1 h. After concentration, the residue mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Silica chromatography (EtOAc/petrol ether; 80:20 to 100:0 then MeOH/EtOAc; 1:99) affords the desired compound

3.38. Compound 40: (1R,2R)-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



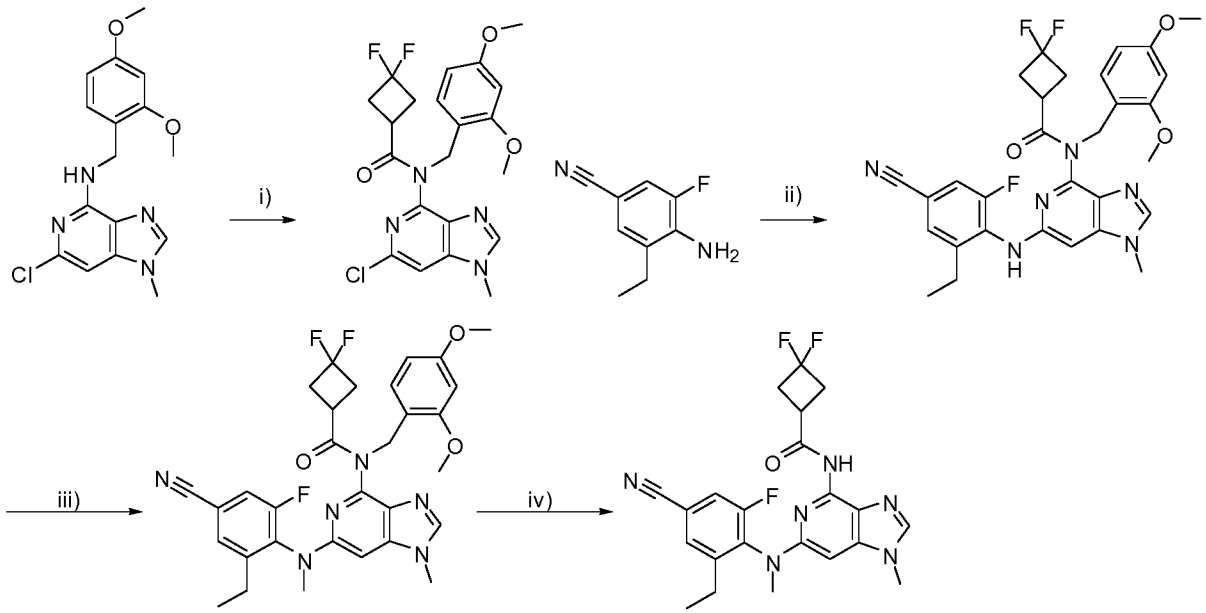
3.38.1. Step i) and ii): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0403] Synthesised following the same conditions used for compound 7 (step ii and iii).

3.38.2. Step iii : (1R,2R)-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0404] Synthesised following the same conditions used for compound 39 (step iv).

3.39. Compound 41: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-3,3-difluorocyclobutanecarboxamide



3.40. Step i : 3,3-Difluoro-cyclobutanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(2,4-dimethoxy-benzyl)-amide

[0405] To 3,3-difluoro-cyclobutanecarboxylic acid (3 eq, 367 mg) in dry DCM (2 mL) at 0 °C is added oxalyl chloride (3 eq, 228 µL) followed by 2 drops of DMF. After 5 min, the amine (1 eq, 300 mg) is added portionwised, followed by pyridine (1 mL), and the mixture warmed to room temperature and stirred for 18 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated. Trituration with petrol ether gave the desired compound.

3.40.1. Step ii : 3,3-Difluoro-cyclobutanecarboxylic acid [6-(4-cyano-2-ethyl-6-fluoro-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(2,4-dimethoxy-benzyl)-amide

A degassed mixture of the amine (1.0 eq, 100 mg), the chloroaryl (1.0 eq, 275 mg), Pd_2dba_3 (0.1 eq, 55 mg), XPhos (0.3 eq, 93 mg) and Cs_2CO_3 (2.5 eq, 499 mg) in dry dioxane (5 mL) is heated at 100 °C for 18 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Purification by silica chromatography (EtOAc/petrol ether; 50:50 to 100:0) affords the desired compound.

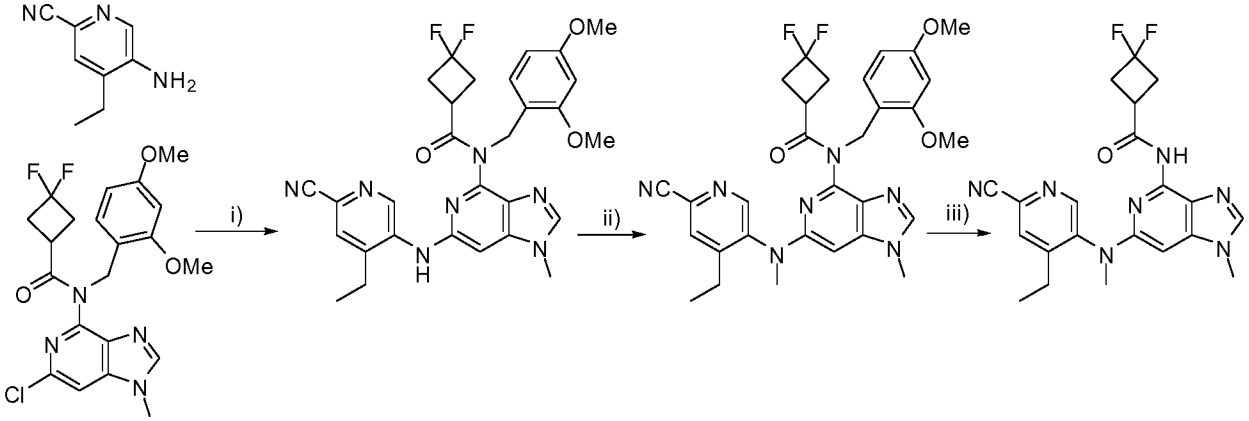
3.40.2. Step iii): 3,3-Difluoro-cyclobutanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(2,4-dimethoxy-benzyl)-amide

[0406] To the amine (1.0 eq, 198 mg) in dry THF (5 mL) is added NaH (1.5 eq, 20 mg). After 5 min, MeI (1.5 eq, 32 µL) is added and the mixture is stirred at room temperature for 18 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used in the next step without further purification.

3.40.3. Step iv : N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-3,3-difluorocyclobutanecarboxamide

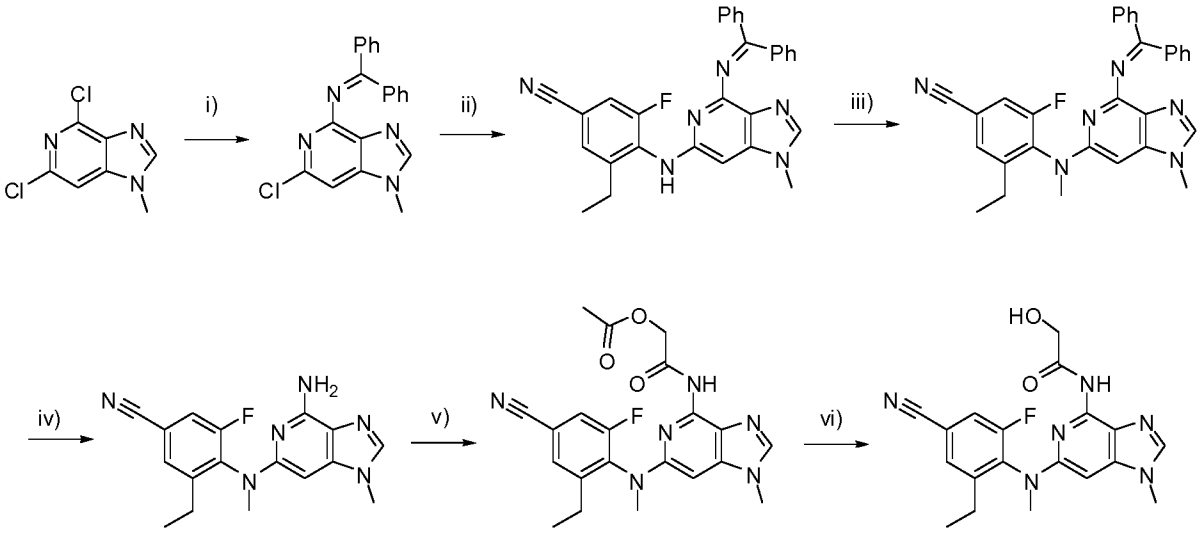
[0407] TFA (2 mL) is added to the crude DMB-protected compound (0.34 mmol) in DCM (2 mL) and stirred at 50 °C for 2 h. The resulting mixture is passed through a SCX column (equilibrated with 5% AcOH in MeOH, eluted with MeOH then with 2M NH_3 in MeOH). Silica chromatography (EtOAc/petrol ether; 80:20) affords the desired compound.

3.41. Compound 42: N-(6-((6-cyano-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-3,3-difluorocyclobutanecarboxamide



[0408] Synthesised following the same conditions used for compound 41 (step ii, iii and iv). Purification by silica chromatography (MeOH/EtOAc; 1:99) affords the desired compound.

3.42. Compound 43: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-hydroxyacetamide



3.42.1. Step i: Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine

[0409] A solution of 4,6-Dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (1.0 eq, 2.0 g), benzophenone imine (1.0 eq, 1.7 mL), and sodium tert-butoxide (1.5 eq, 1.4 g) in dry toluene (40 mL) is degassed under nitrogen flow. To this solution is added $Pd(OAc)_2$ (0.1 eq, 225 mg) and BINAP (0.3 eq, 1.8 g) and the mixture is degassed again and then stirred at 80 °C for 2 h. The mixture is diluted with EtOAc and filtered through a celite pad. Solids are thoroughly washed with EtOAc. The filtrate is washed with a saturated solution of $NaHCO_3$. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 0/100 followed by EtOAc/MeOH: 100/0 to 95/5) to afford the desired product.

3.42.2. Step ii): 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzonitrile

[0410] A mixture of Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine (1.0 eq, 2.2 g), 4-Amino-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 1.05 g), and Cs_2CO_3 (2.5 eq, 5.2 g) in dry toluene (70 mL) are charged in a round bottom flask and degassed under nitrogen flow. To this solution is added Pd_2dba_3 (0.1 eq, 580 mg) and XPhos (0.3 eq, 915 mg) and the mixture is degassed again and then stirred at 130 °C for 16 h.

[0411] The mixture is diluted with DCM and filtered through a celite pad. Solids are thoroughly washed with DCM. The filtrate is washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 0/100 followed by EtOAc/MeOH: 100/0 to 95/5) to afford the desired product.

3.42.3. Step iii: 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzonitrile

[0412] To a mixture of 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 500 mg) and NaH (3.0 eq, 125 mg) in dry THF (20 mL) is added iodomethane (3.0 eq, 200 µL). The mixture is stirred at room temperature. After 2 h, the mixture is diluted with EtOAc and neutralized by addition of water. The organic layer is then washed with sat $NaHCO_3$, filtered through a phase separator and concentrated. The residue is used without further purification.

3.42.4. Step iv: 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile

[0413] To a mixture of 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 460 mg) in dry THF (5 mL) is added an aqueous solution of hydrochloric acid (1.0 M, 5 mL) and the mixture is then stirred at room temperature for 30 min. The mixture is diluted with water and EtOAc. The organic layer is discarded. The aqueous layer is basified with a solution of NaOH 1N and extracted with DCM. The organic layer is filtered through a phase separator and concentrated. The residue is used in the next step without further purification.

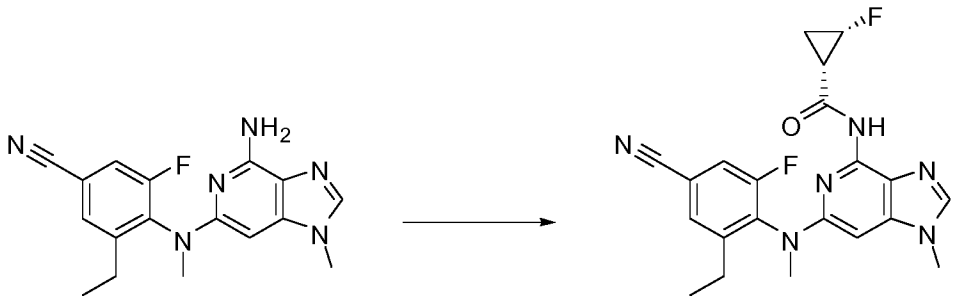
3.42.5. Step v: Acetic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-ylcarbamoyl}-methyl ester

[0414] To a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) and pyridine (2.0 eq, 25 µL) in DCM (2 mL) is added Acetic acid chlorocarbonylmethyl ester (1.2 eq, 26 mg) at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The residue is used without further purification.

3.42.6. Step vi: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2- hydroxyacetamide

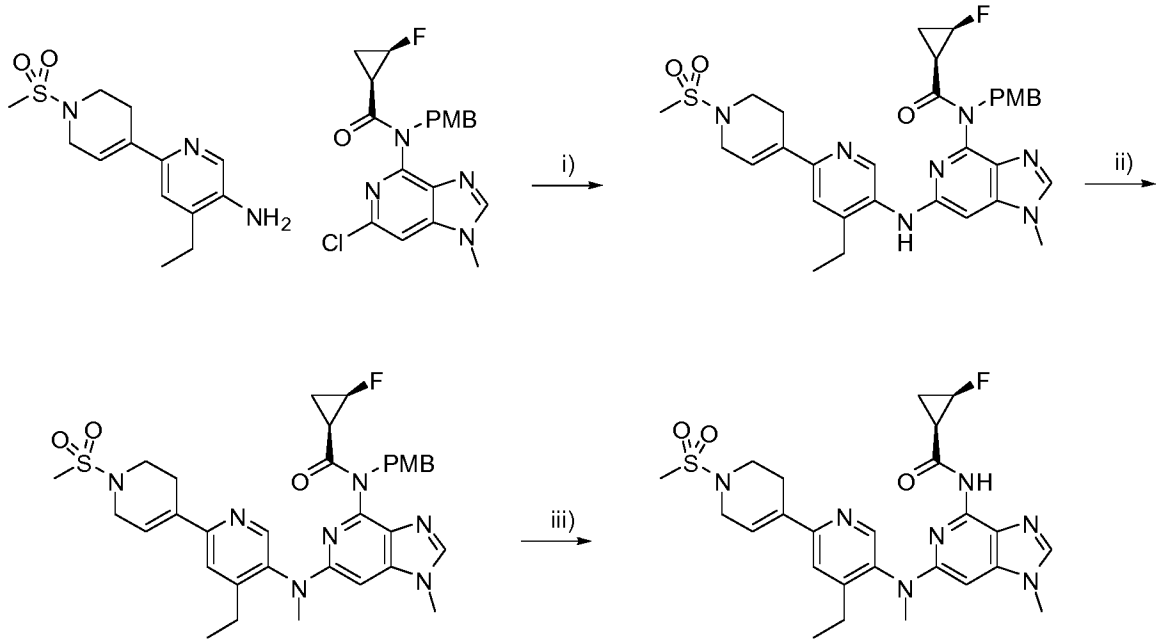
[0415] A mixture of Acetic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-ylcarbamoyl}-methyl ester (1.0 eq, 140 mg) and K_2CO_3 (1 spatula) in MeOH/H_2O (2/2 mL) is stirred at room temperature for 2 h. Volatiles are removed *in vacuo*. The residue is diluted in DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The crude is purified by silica chromatography (DCM/MeOH: 100/0 to 96/4) to yield the desired product.

3.43. Compound 44: (1S,2S)-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



[0416] To a solution of (1S,2S)-2-fluoro-cyclopropanecarboxylic acid (2.0 eq, 20 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by silica chromatography (DCM/MeOH: 100/0 to 96/4), followed by SCX-3 column to yield the desired product.

3.44. Compound 45: (1S,2R)-N-(6-((4-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide



3.44.1. Step i : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0417] A solution of (1R,2R)-2-fluoro-cyclopropanecarboxylic acid (6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-(4-methoxy-benzyl)-amide (1.2 eq, 200 mg), 4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-ylamine (1.0 eq, 120 mg), Cs_2CO_3 (2.5 eq, 350 mg) in dry 1,4-dioxane

(3 mL) is degassed under nitrogen flow. To this solution is added Pd_2dba_3 (0.1 eq, 36 mg) and XPhos (0.3 eq, 57 mg) and the resulting mixture is degassed again and stirred at 100 °C for 3 h. The mixture is diluted with DCM, filtered through a celite pad. The filtrate is washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 0/100, followed by EtOAc/MeOH: 100/0 to 95/5) to afford the desired product.

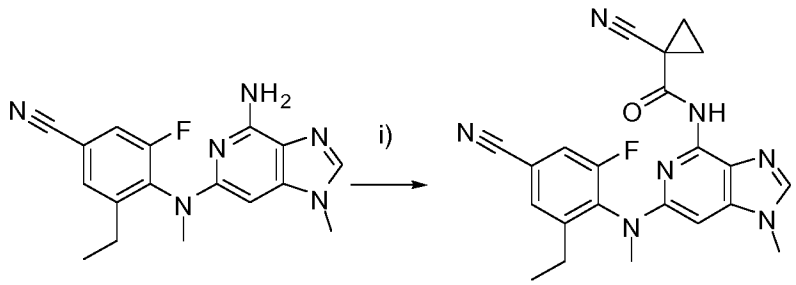
3.44.2. Step ii): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0418] Synthesised following the same conditions used for compound 35 (step iii).

3.44.3. Step iii : (1S,2R)-N-(6-((4-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide

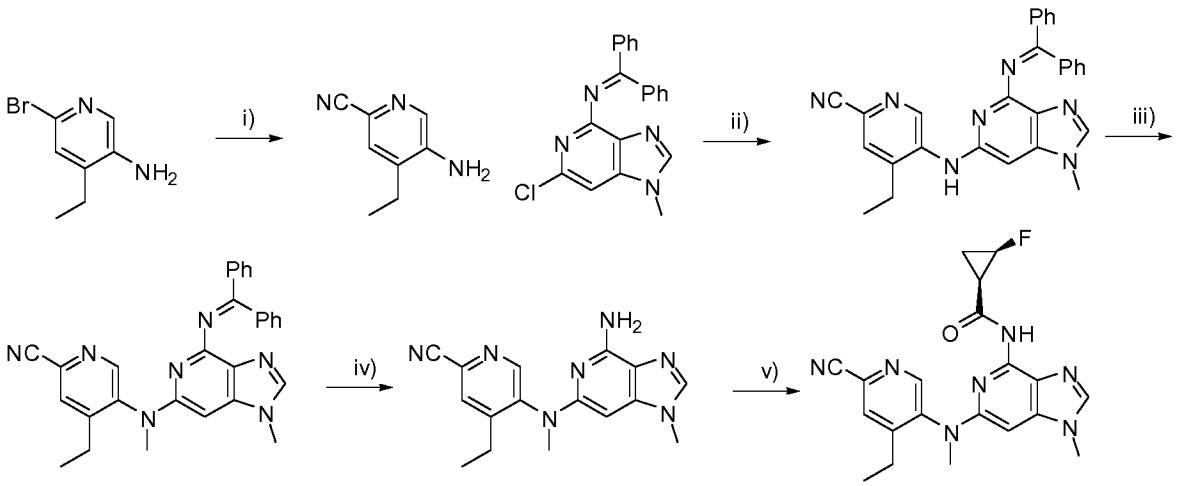
[0419] (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-ethyl-1'-methanesulfonyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide (1.0 eq, 130 mg) is dissolved in TFA (3 mL) and the mixture is heated at 80 °C for 16 h. The mixture is carefully neutralized with a saturated solution of $NaHCO_3$, and the product is extracted with DCM. The organic layer is filtered through a phase separator and concentrated. The residue is purified by SCX-3 column to afford the desired product.

3.45. Compound 46: 1-cyano-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



[0420] To a solution of 1-cyano-cyclopropanecarboxylic acid (2.0 eq, 33 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.46. Compound 47: (1R,2R)-N-(6-((6-cyano-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.46.1. Step i): 5-Amino-4-ethyl-pyridine-2-carbonitrile

[0421] A mixture of 6-bromo-4-ethyl-pyridin-3-ylamine (1.0 eq, 1 g) and $Zn(CN)_2$ (1.6 eq, 926 mg) and $Pd(PPh_3)_4$ (0.1 eq, 578 mg) in dry DMF (15 mL) is heated at 150 °C for 20 min in a microwave reactor. The mixture is diluted with EtOAc and washed with aq. sat. $NaHCO_3$. The aqueous is further extracted with EtOAc (2x). The combined organics is washed with brine, dried and concentrated. Silica chromatography (EtOAc/petrol ether; 20:80 to 50:50) affords the desired compound.

3.46.2. Step ii): 5-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-4-ethyl-pyridine-2-carbonitrile

[0422] A degassed mixture of the amine (1.1 eq, 606 mg), the chloroaryl (1.0 eq, 1.3 g), $Pd(OAc)_2$ (0.2 eq, 168 mg), BINAP (0.3 eq, 704 mg) and Cs_2CO_3 (4.5 eq, 5.5 g) in dry dioxane (5 mL) in a sealed tube is heated at 110 °C for 2 h. The resulting mixture is diluted with 10% MeOH in EtOAc and washed with water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated. Purification by silica chromatography (EtOAc/petrol ether; 20:80 to 100:0 then MeOH/EtOAc; 1:99 to 5:95) affords the desired compound.

3.46.3. Step iii): 5-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-4-ethyl-pyridine-2-carbonitrile

[0423] To the amine (1.0 eq, 2.7 g) in dry THF (5 mL) is added NaH (2.0 eq, 472 mg). After 5 min, MeI (2.0 eq, 0.73 mL) is added and the mixture is stirred at room temperature for 2 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used directly in the next step without further purification

3.46.4. Step iv): 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-ethyl-pyridine-2-carbonitrile

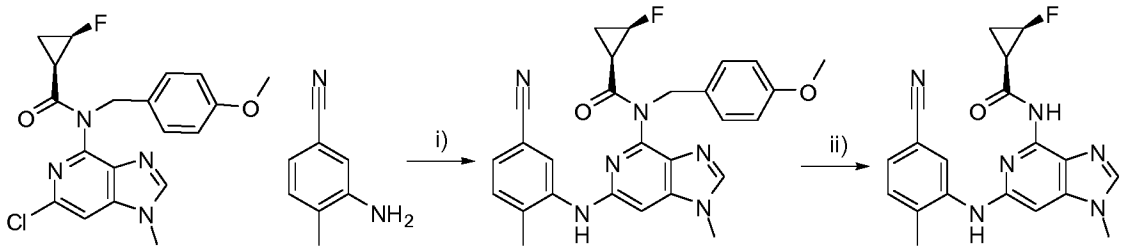
[0424] To a solution of the crude benzophenonimine in THF (25 mL) is added aq. 2M HCl solution (25 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with

EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated to afford the desired compound.

3.46.5. Step v): (1R,2R)-N-(6-((6-cyano-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0425] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 377 mg) in dry DCM (30 mL) at 0 °C is added oxalyl chloride (1.5 eq, 0.31 mL) followed by 3-4 drops of DMF. After 5 min, a suspension of the amine (1 eq, 740 mg) in dry DCM (10 mL) is added portionwised, followed by pyridine (5 mL), and the mixture is stirred for 4 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated. Silica chromatography (EtOAc/petrol ether; 75:25 to 100:0 then MeOH/EtOAc; 3:97) affords the desired compound.

3.47. Compound 48: (1R,2R)-N-(6-(5-cyano-2-methylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



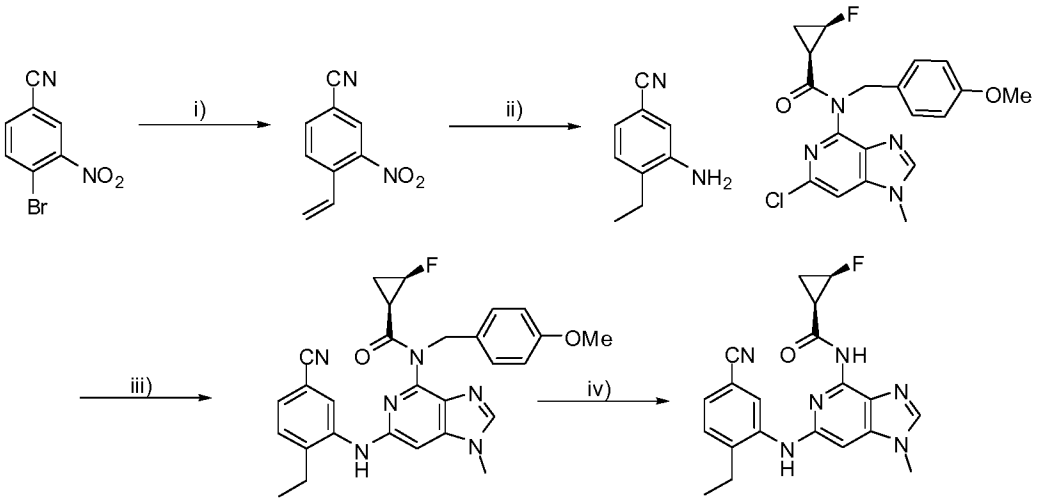
3.47.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(5-cyano-2-methyl-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0426] Synthesised following the same conditions used for compound 41 (step ii).

3.47.2. Step ii): (1R,2R)-N-(6-(5-cyano-2-methylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0427] Synthesised following the same conditions used for compound 39 (step iv). Silica chromatography (MeOH/EtOAc; 5:95) affords the desired compound.

3.48. Compound 49: (1R,2R)-N-(6-(5-cyano-2-ethylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.48.1. Step i : 3-Nitro-4-vinyl-benzonitrile

[0428] A mixture of 4-bromo-3-nitro-benzonitrile (1.0 eq, 1.0 g), potassium vinyl trifluoroborate (1.5 eq, 0.89 g), $PdCl_2$(dppf).DCM (0.05 eq, 201 mg), K_2CO_3 (3.0 eq, 1.82 g) in THF/water (10:1; 20 mL) is heated at 80 °C. After 1 h, the resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is used as such in the next step.

3.48.2. Step ii : 3-Amino-4-ethyl-benzonitrile

[0429] To the crude nitro-vinylaryl in EtOH (20 mL) under 1 atm of hydrogen is added Pd/C (10%, 0.1 eq, 468 mg) and the mixture is stirred at room temperature for 24 h. After filtration on Celite and concentration, purification by silica chromatography (EtOAc/petrol ether; 20:80) affords the desired compound.

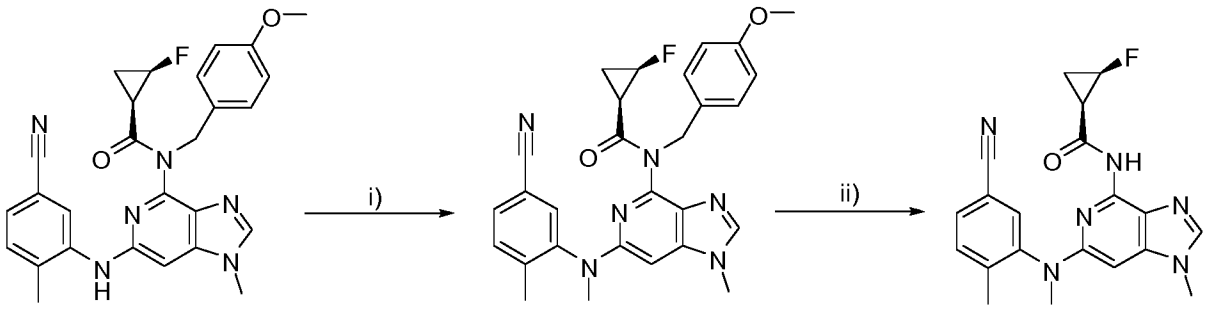
3.48.3. Step iii: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(5-cyano-2-ethyl-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0430] Synthesised following the same conditions used for compound 41 (step ii).

3.48.4. Step iv: (1R,2R)-N-(6-(5-cyano-2-ethylphenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0431] Synthesised following the same conditions used for compound 39 (step iv). Silica chromatography (MeOH/EtOAc; 5:95) affords the desired compound.

3.49. Compound 50: (1R,2R)-N-(6-((5-cyano-2-methylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



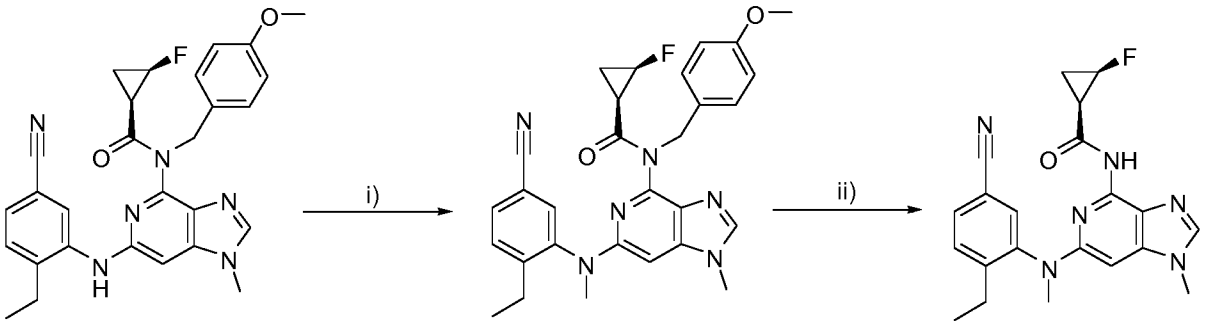
3.49.1. Step i: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(5-cyano-2-methyl-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0432] Synthesised following the same conditions used for compound 7 (step iii).

3.49.2. Step ii : (1R,2R)-N-(6-((5-cyano-2-methylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0433] Synthesised following the same conditions used for compound 39 (step iv). Silica chromatography (MeOH/EtOAc; 4:94 to 10:90) affords the desired compound.

3.50. Compound 51: (1R,2R)-N-(6-((5-cyano-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



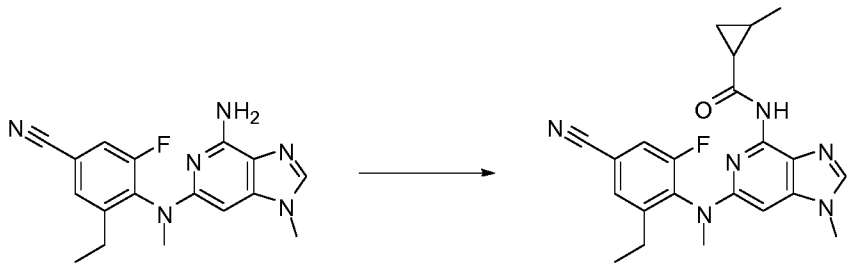
3.50.1. Step i : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(5-cyano-2-ethyl-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0434] Synthesised following the same conditions used for compound 7 (step iii).

3.50.2. Step ii : (1R,2R)-N-(6-((5-cyano-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

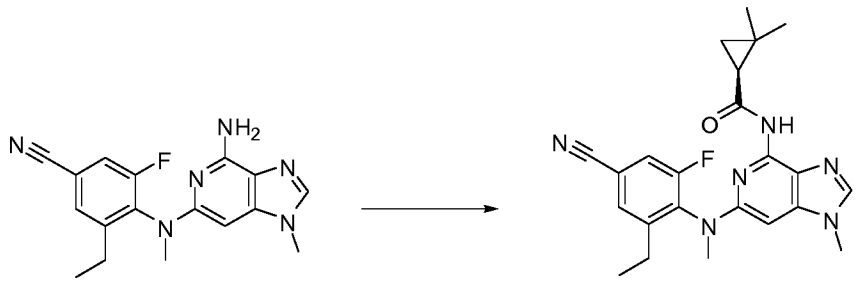
[0435] Synthesised following the same conditions used for compound 39 (step iv). Silica chromatography (MeOH/EtOAc; 4:94 to 10:90) affords the desired compound.

3.51. Compound 52: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-methylcyclopropanecarboxamide



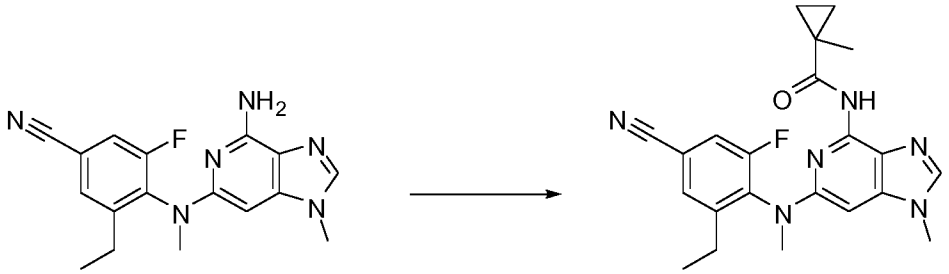
[0436] To a solution of 2-methyl-cyclopropanecarboxylic acid (2.0 eq, 19 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.52. Compound 53: (S)-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2,2-dimethylcyclopropanecarboxamide



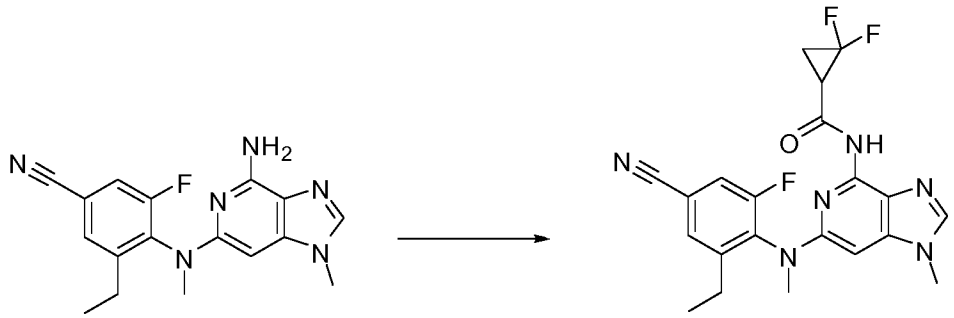
[0437] To a solution of (S)-2,2-dimethyl-cyclopropanecarboxylic acid (2.0 eq, 22 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.53. Compound 54: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-1-methylcyclopropanecarboxamide



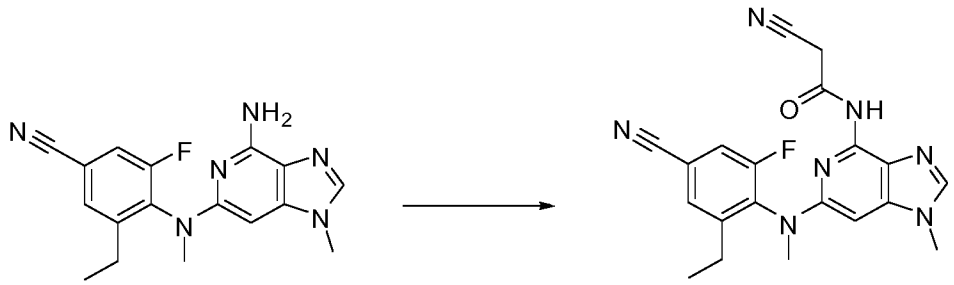
[0438] To a solution of 1-methyl-cyclopropanecarboxylic acid (2.0 eq, 30 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.54. Compound 55: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2,2-difluorocyclopropanecarboxamide



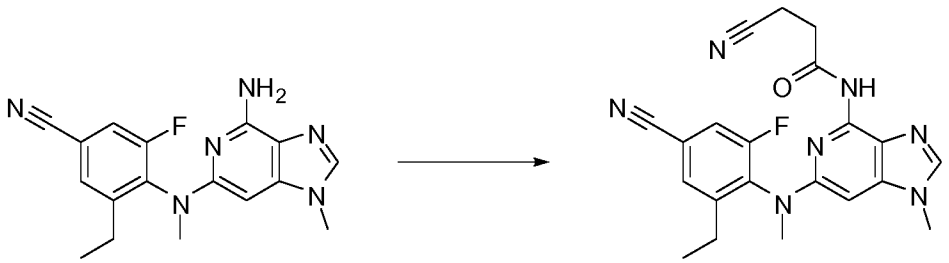
[0439] To a solution of 2,2-difluoro-cyclopropanecarboxylic acid (2.0 eq, 37 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 25 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.55. Compound 56: 2-cyano-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)acetamide



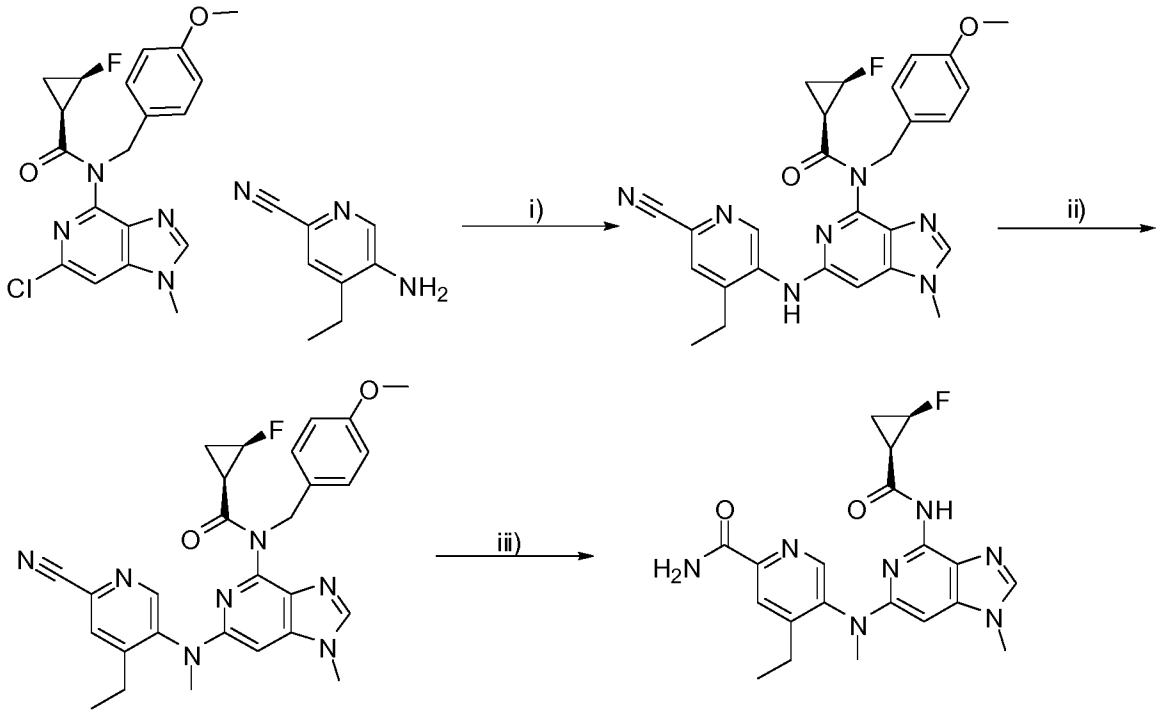
[0440] To a solution of cyano-acetic acid (2.0 eq, 51 mg) in DCM (1.5 mL) is added oxalyl chloride (2.0 eq, 50 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 100 mg) in DCM (1.5 mL) is added. Pyridine (2.0 eq, 50 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.56. Compound 57: 3-cyano-N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)propanamide



[0441] To a solution of 3-cyano-propionic acid (2.0 eq, 59 mg) in DCM (1.5 mL) is added oxalyl chloride (2.0 eq, 50 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 100 mg) in DCM (1.5 mL) is added. Pyridine (2.0 eq, 50 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.57. Compound 58: 4-ethyl-5-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)picolinamide



3.57.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(6-cyano-4-ethyl-pyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0442] Synthesised following the same conditions used for compound 41 (step ii). Silica chromatography (EtOAc/petrol ether; 80:20 to 100:0 then MeOH/EtOAc; 4:96) affords the desired compound.

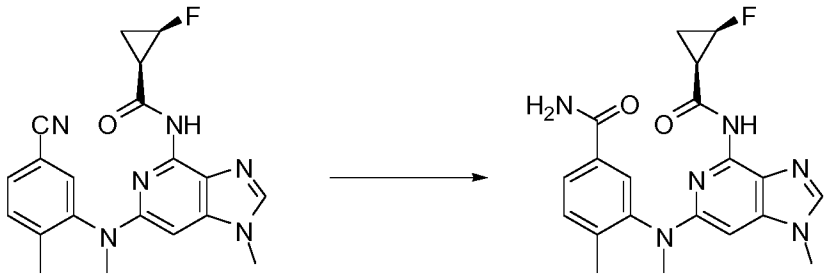
3.57.2. Step ii): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-4-ethyl-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0443] Synthesised following the same conditions used for compound 7 (step iii).

3.57.3. Step iii): 4-ethyl-5-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)picolinamide

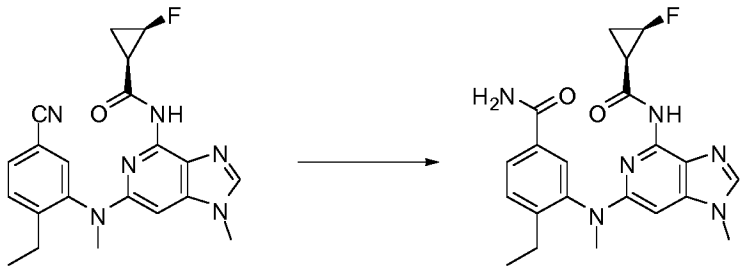
[0444] A solution of the crude PMB-protected compound (0.50 mmol) in TFA is stirred at 80 °C for 20 h. After concentration, the residue mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Silica chromatography (1:99 to 5:95 MeOH/DCM) followed by preparative HPLC affords the desired compound.

3.58. Compound 59: 3-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-4-methylbenzamide



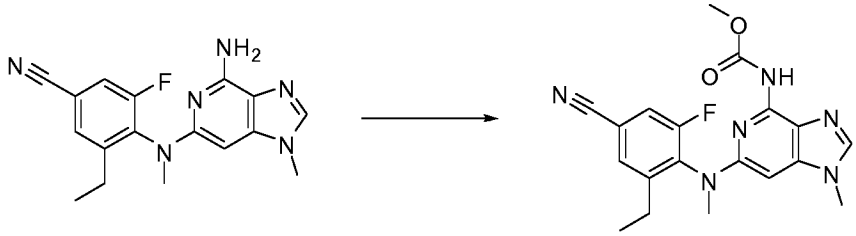
[0445] To the nitrile-aryl (1 eq, 10 mg) in EtOH/DMSO (2:1; 2 mL) is added aq. 1M NaOH (100 µL) and H_2O_2 (35% in water, 60 µL) and the mixture is stirred at 50 °C for 1.5 h. The resulting mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC to afford the desired compound.

3.59. Compound 60: 4-ethyl-3-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)benzamide



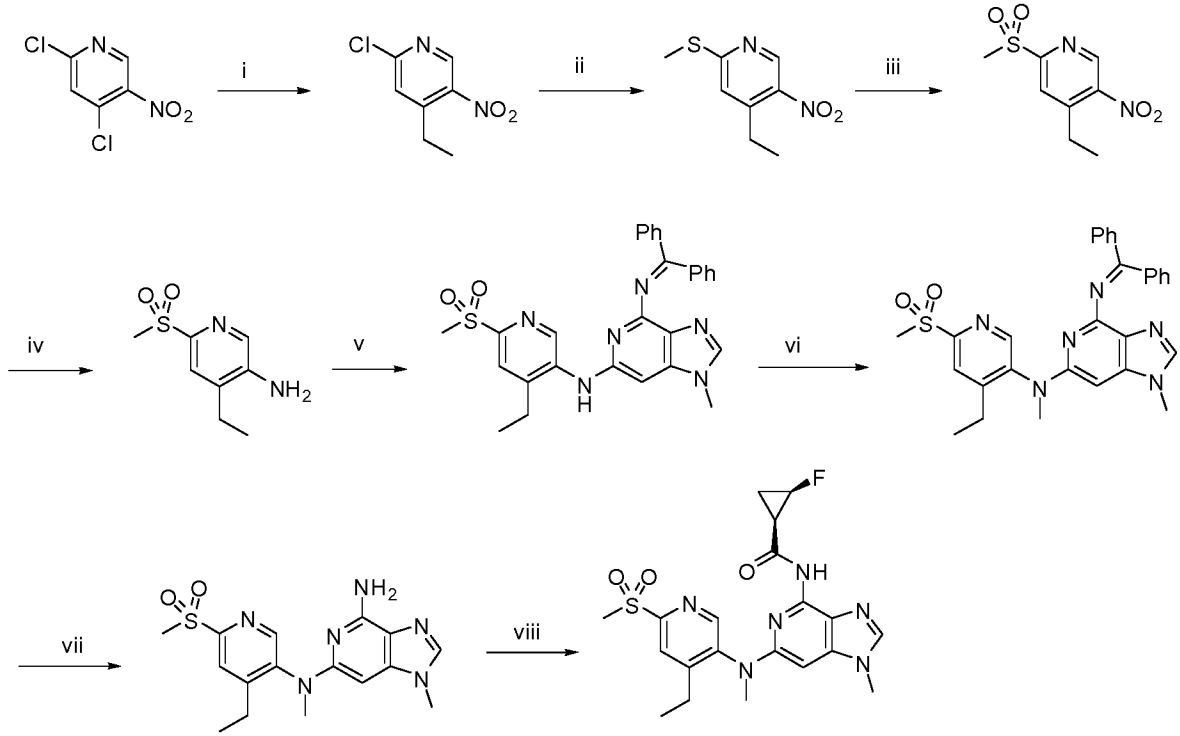
[0446] Synthesised following the same conditions used for Compound 59.

3.60. Compound 61: methyl 6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-ylcarbamate



[0447] To a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 g, 75 mg) and pyridine (3.0 eq, 60 µL) in DCM (2 mL) is added methyl chloroformate (3.0 eq, 60 µL) at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 0/100, followed by EtOAc/MeOH: 100/0 to 96/4) to afford the desired product.

3.61. Compound 62: (1R,2R)-N-(6-((4-ethyl-6-(methylsulfonyl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.61.1. Step i): 2-Chloro-4-ethyl-5-nitro-pyridine

[0448] In a round bottom flask, 2,4-Dichloro-5-nitro-pyridine (1.0 eq, 500 mg), ethylboronic acid (1.1 eq, 210 mg) and Na_2CO_3 (1.17 eq, 320 mg) are suspended in Toluene (3.5 mL, 7 vol), heptane (1.5 mL, 3 vol) and water (2.0 mL, 4 vol) and degassed under nitrogen flow for 10 min. $Pd(dppf)CL_2$ (0.04 eq, 82 mg) is added and the reaction is stirred at 85 °C for 24 h. The reaction mixture is cooled to room temperature and diluted with EtOAc, filtered through a SEITZ filter pad (K100, d=60 mm). Solids are thoroughly washed with EtOAc. The filtrate is washed with a saturated solution of $NaHCO_3$. The organic layer is dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue is purified by silica chromatography (Petroleum ether/EtOAc: 100/0 to 95/5) to afford the desired product.

3.61.2. Step ii): 4-Ethyl-2-methylsulfanyl-5-nitro-pyridine

[0449] In a round bottom flask containing methylmercaptan (10 eq, 1.5 g) is added a solution of 2-Chloro-4-ethyl-5-nitro-pyridine (1.0 eq, 400 mg) in EtOH (10 mL) and MeOH (10 mL). The resulting solution is stirred at room temperature. After 4 h, the mixture is diluted with EtOAc and water. The

aqueous layer is further extracted with EtOAc. The combined organic layers are dried (Na_2SO_4), filtered and concentrated. The product is used without further purification.

3.61.3. Step iii): 4-Ethyl-2-methanesulfonyl-5-nitro-pyridine

[0450] To a solution of 4-ethyl-2-methylsulfanyl-5-nitro-pyridine (1.0 eq, 400 mg) in THF (20 mL) is carefully added TFA (3 mL), followed by carefull addition of mCPBA (3.0 eq, 1.0 g). The resulting mixture is stirred at room temperature for 20 min. The mixture is diluted with EtOAc and water. The two phases are separated and the organic layer is dried (Na_2SO_4), filtered and concentrated. The resulting solids are triturated in DIPE and filtered to yield the desired product.

3.61.4. Step iv): 4-Ethyl-6-methanesulfonyl-pyridin-3-ylamine

[0451] To a solution of 4-Ethyl-2-methanesulfonyl-5-nitro-pyridine (1.0 eq, 320 mg) in MeOH (10 mL) is added zinc powder (10.0 eq, 910 mg), NH_4Cl (cat.) and formic acid (2 mL). The resulting mixture is heated to 80 °C for 30 min. The mixture is cooled to room temperature and filtered through celite and solids are washed with DCM. The filtrate is washed with a saturated solution of $NaHCO_3$, filtered through a hydrophobic frit and concentrated. The product is used as such in the next step.

3.61.5. Step v): N4-Benzhydrylidene-N6-(4-ethyl-6-methanesulfonyl-pyridin-3-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0452] A mixture of benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine (1.2 eq, 415 mg), 4-Ethyl-6-methanesulfonyl-pyridin-3-ylamine (1.0 eq, 200 mg), and Cs_2CO_3 (2.5 eq, 815 mg) in dry toluene (10 mL) are charged in a sealed tube and degassed under nitrogen flow. To this solution is added Pd_2dba_3 (0.1 eq, 90 mg) and XPhos (0.3 eq, 140 mg) and the mixture is degassed again and stirred at 130 °C for 3 h. The mixture is filtered through a celite pad, and solids are thoroughly washed with EtOAc. The filtrate is washed with a saturated solution of $NaHCO_3$. The organic layer is dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica chromatography (EP/EtOAC: 100/0 to 0/100) to afford the desired product.

3.61.6. Step vi): N4-Benzhydrylidene-N6-(4-ethyl-6-methanesulfonyl-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0453] Synthesised following the same conditions used for compound 43 (step iii).

3.61.7. Step vii): N6-(4-Ethyl-6-methanesulfonyl-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

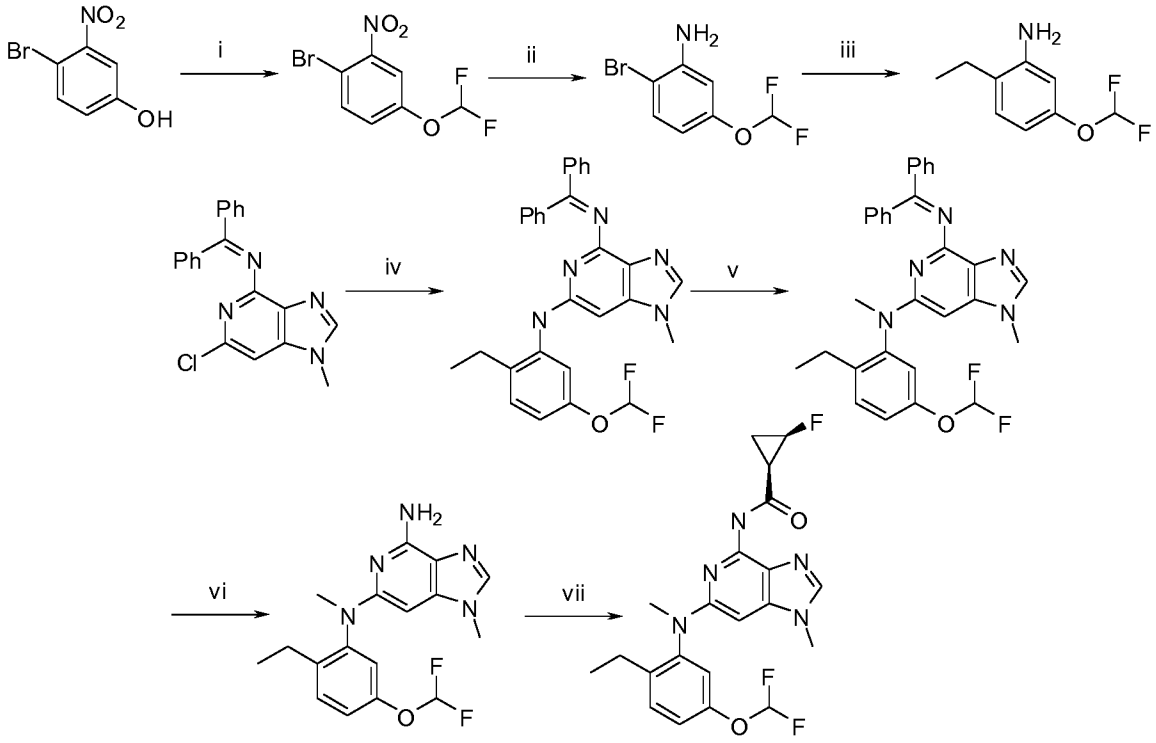
[0454] Synthesised following the same conditions used for compound 43 (step iv).

3.61.8. Step viii): (1R,2R)-N-(6-((4-ethyl-6-(methylsulfonyl)pyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0455] To a solution of (1R,2R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 22 mg) in DCM (1 mL) is added oxalyl chloride (1.5 eq, 20 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (3.0 eq, 35 µL) is added and the resulting mixture is stirred

at room temperature for 2 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 0/100) to yield the desired product.

3.62. Compound 63: (1R,2R)-N-(6-((5-(difluoromethoxy)-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.62.1. Step i): 1-Bromo-4-difluoromethoxy-2-nitro-benzene

[0456] Diethyl(bromodifluoromethyl)phosphonate (2 eq, 1.64mL) is added to a cooled (-30 °C) solution of 4-Bromo-3-nitro-phenol (1 eq, 1.0 g) and KOH (20 eq, 5.17 g) in MeCN/water (46 mL; 1:1) and the reaction mixture is allowed to warm to room temperature. After 30 min, the mixture is diluted with Et_2O, the organic phase is separated and the water phase is washed with a further amount of Et_2O. The combined organics are dried and concentrated. The residue is purified by silica chromatography (5-50 % EtOAc in petroleum ether) to give the desired product.

3.62.2. Step ii): 2-Bromo-5-difluoromethoxy-phenylamine

[0457] Formic acid (1.5 mL) is added slowly to an ice cooled solution of nitro aryl (1 eq, 623 mg), Zinc (10 eq, 1.52 g) and a catalytic amount of NH_4Cl in MeOH (8 mL). After the addition the ice bath is removed and the mixture is stirred 10 min at room temperature before it is heated to 50°C. After 45 min, the solids are filtered off and the solid is washed with MeOH. The filtrates are concentrated and the residue is diluted with sat. $NaHCO_3$ and DCM. The organic layer is separated and concentrated. The obtained crude is purified by silica chromatography (2-50% EtOAc in petroleum ether) to give the desired product.

3.62.3. Step iii): 5-Difluoromethoxy-2-ethyl-phenylamine

[0458] To a degassed solution of aryl bromide (1 eq, 740 mg), Pd(dppf)CL_2.DCM (0.10 eq, 254 mg), and Cs_2CO_3 (6 eq, 6.10 g) in DMF (12 mL) are added water (150 µL) and a solution of triethylborane (1M in hexane (1.5 eq, 4.7 mL) in DMF (3 mL). The mixture is heated at 60°C for 30 min. The mixture is concentrated and the residue is diluted with 40 mL EtOAc and the organic layer is washed with 20 mL sat. $NaHCO_3$ and 3 times 20 mL water, dried and concentrated. The product is purified by silica chromatography (2-30% EtOAc in petroleum ether) to give the desired product.

3.62.4. Step iv): N4-Benzhydrylidene-N6-(5-difluoromethoxy-2-ethyl-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0459] To a degassed solution of Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine (1 eq, 315 mg), aniline (step iii, 1eq, 170 mg), Cs_2CO_3 (5 eq, 1.47 g) in dioxane (6.5 mL) are added $Pd(OAc)_2$ (0.2 eq, 41 mg) and BINAP (0.2 eq, 113 mg). The mixture is degassed again and heated to 100°C. After 2h the mixture is concentrated and the residue is diluted with DCM and sat. $NaHCO_3$. The organic layer is separated and concentrated and purified by silica chromatography (20-100% EtOAc in petroleum ether) to give a crude product that is used in the next step without further purification.

3.62.5. Step v: N4-Benzhydrylidene-N6-(5-difluoromethoxy-2-ethyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0460] NaH (60% in mineral oil, 2.5 eq, 122 mg) is added to a solution of crude amine (step iv, 1 eq, 603 mg) in THF (6 mL). After 30 min stirring at room temperature MeI (1.5 eq, 114 µL) is added and the reaction is left on overnight. The mixture is quenched with water and concentrated. The residue is diluted with sat. $NaHCO_3$ and DCM. The organic layer is separated and concentrated to obtain a crude product that is used as such in the next step without further purification.

3.62.6. Step vi: N6-(5-Difluoromethoxy-2-ethyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

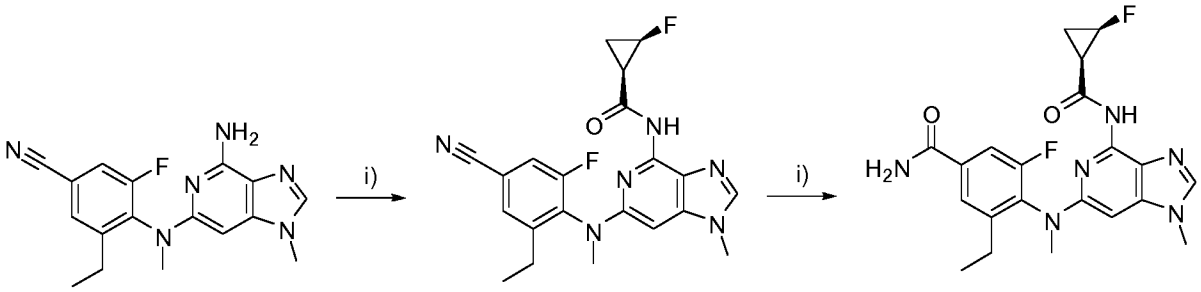
[0461] Crude N4-Benzhydrylidene-N6-(5-difluoromethoxy-2-ethyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (step v) is stirred in THF (5 mL) and 1N HCl (5mL). After 1 h the mixture is diluted with EtOAc. The aqueous layer is separated, basicified with 1N NaOH, diluted with DCM and the organic layer is separated to give the crude product that is used in the next step without further purification.

3.62.7. Step vii): (1R,2R)-N-(6-((5-(difluoromethoxy)-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0462] Oxalyl chloride (1.5 eq, 86 µL) is added to an ice cooled solution of (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (1.5 eq, 104 mg) in DCM (3 mL). 2 drops of DMF are added. After 30 min are added a solution of amine (step vi, 1 eq, 230 mg) in DCM (2 mL) and pyridine (3 eq, 158 µL). 150 µL pyridine is added after 1h. After 2 h the reaction mixture is diluted with DCM and sat. $NaHCO_3$. The organic layer is separated and concentrated. The obtained residue is purified by silica chromatography (0-

20% MeOH in EtOAc) to give a crude product that is further purified by preparative HPLC to give the desired product.

3.63. Compound 64: 3-ethyl-5-fluoro-4-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)benzamide



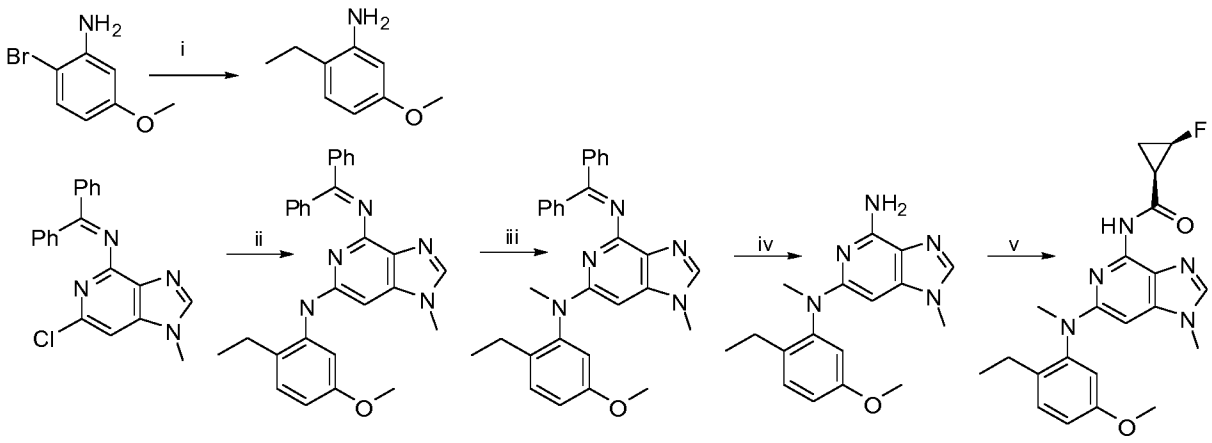
3.63.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0463] To a solution of (1R,2R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 36 mg) in DCM (1 mL) is added oxalyl chloride (1.5 eq, 30 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 75 mg) in DCM (1 mL) is added. Pyridine (2.0 eq, 40 µL) is added and the resulting mixture is stirred at room temperature for 2 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by SCX-3 column to yield the desired product.

3.63.2. Step ii): 3-ethyl-5-fluoro-4-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)benzamide

[0464] To a solution of (1R,2R)-2-fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (1.0 eq, 40 mg) in EtOH (1.0 mL) and DMSO (0.25 mL) is added a solution of 1N NaOH (130 µL) and a 35 % aqueous solution of H_2O_2 (100 µL). the resulting mixture is stirred at 50 °C for 2h. The volatiles are removed *in vacuo* and the residue is diluted in DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The product is purified by preparative HPLC.

3.64. Compound 65: (1R,2R)-N-(6-((2-ethyl-5-methoxyphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.64.1. Step i: 2-Ethyl-5-methoxy-phenylamine

[0465] Synthesized following the same conditions used for compound 63 (step iii)

3.64.2. Step ii: N4-Benzhydrylidene-N6-(2-ethyl-5-methoxy-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0466] Synthesized following the same conditions used for compound 63 (step iv).

3.64.3. Step iii: N4-Benzhydrylidene-N6-(2-ethyl-5-methoxy-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0467] Synthesized following the same conditions used for compound 63 (step v).

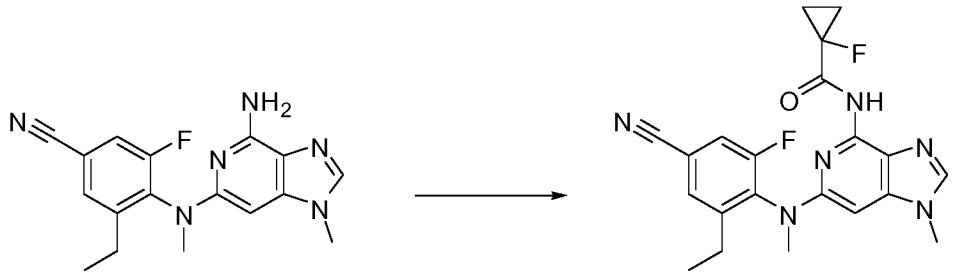
3.64.4. Step iv: N6-(2-Ethyl-5-methoxy-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0468] Synthesized following the same conditions used for compound 63 (step vi)

3.64.5. Step v: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(2-ethyl-5-methoxy-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

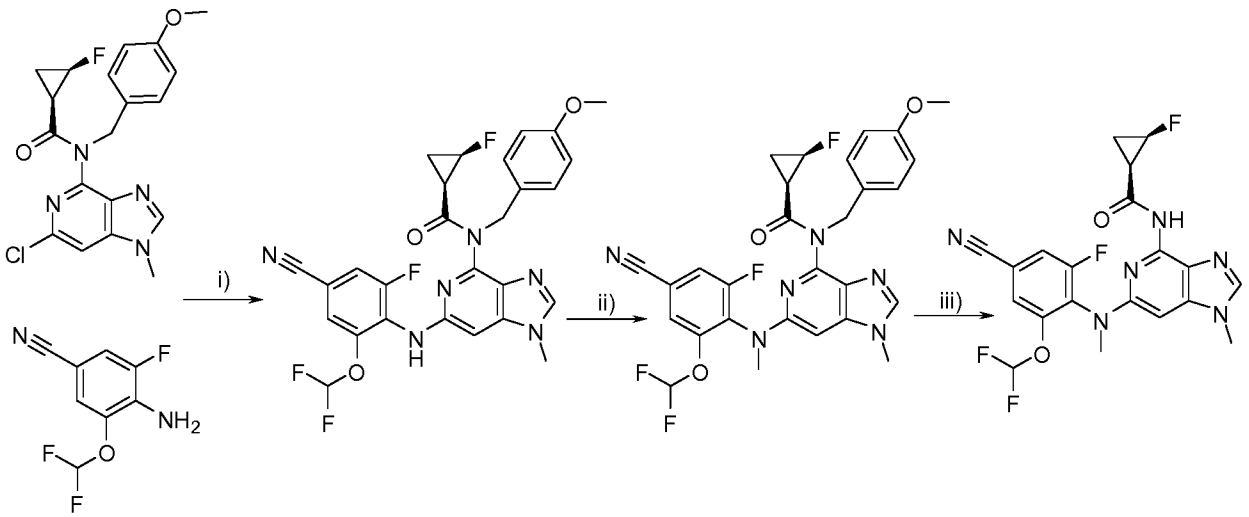
[0469] Oxalyl chloride (1.5 eq, 46 µL) is added to an ice cooled solution of (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (1.5 eq, 56 mg) in DCM (2 mL). 2 drops of DMF are added. After 30 min are added a solution of amine (step iv, 1 eq, 110 mg) in DCM (2 mL) and pyridine (3 eq, 86 µL). After 3 h the reaction mixture is diluted with DCM and sat. $NaHCO_3$. The organic layer is separated and concentrated. The obtained residue is stirred in 2N (NH_3 in MeOH). After 30 min the mixture is concentrated and the residue is diluted with DCM and sat. $NaHCO_3$. The organic layer is separated and concentrated. The residue is purified by silica chromatography (0-10% MeOH in EtOAc) to give a crude product that is further purified by trituration with EtOAc to give the desired product.

3.65. Compound 66: N-(6-((4-cyano-2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-1-fluorocyclopropanecarboxamide



[0470] To a solution of 1-fluoro-cyclopropanecarboxylic acid (2.0 eq, 30 mg) in DCM (1 mL) is added oxalyl chloride (2.0 eq, 25 µL) at 0 °C, followed by 2 drops of DMF. After 30 min, a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 50 mg) in DCM (1 mL) is added. Pyridine (3.0 eq, 35 µL) is added and the resulting mixture is stirred at room temperature for 16 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by preparative HPLC to yield the desired product.

3.66. Compound 67: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.66.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(4-cyano-2-difluoromethoxy-6-fluoro-phenylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-(4-methoxy-benzyl)-amide

[0471] A degassed mixture of the amine (1.1 eq, 100 mg), the chloroaryl (1.0 eq, 175 mg), $Pd(OAc)_2$ (0.2 eq, 20 mg), BINAP (0.3 eq, 87 mg) and Cs_2CO_3 (4.5 eq, 661 mg) in dry dioxane (2 mL) in a sealed tube is heated at 110 °C for 2 h. The resulting mixture is diluted with EtOAc, washed with water, brine, dried and concentrated. Purification by silica chromatography (EtOAc/petrol ether; 20:80 to 100:0) affords the desired product.

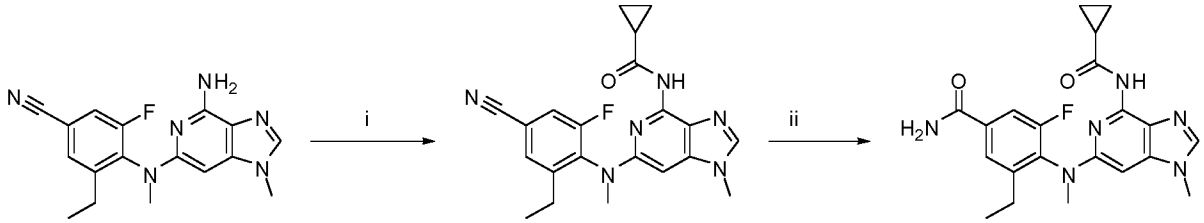
3.66.2. Step ii : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-(4-methoxy-benzyl)-amide

[0472] Synthesised following the same conditions used for compound 7 (step iii).

3.66.3. Step iii : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0473] Synthesised following the same conditions used for Compound 39 (step iv). Silica chromatography (EtOAc/petrol ether; 50:50 to 100:0) affords the desired compound.

3.67. Compound 68: 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethyl-5-fluorobenzamide



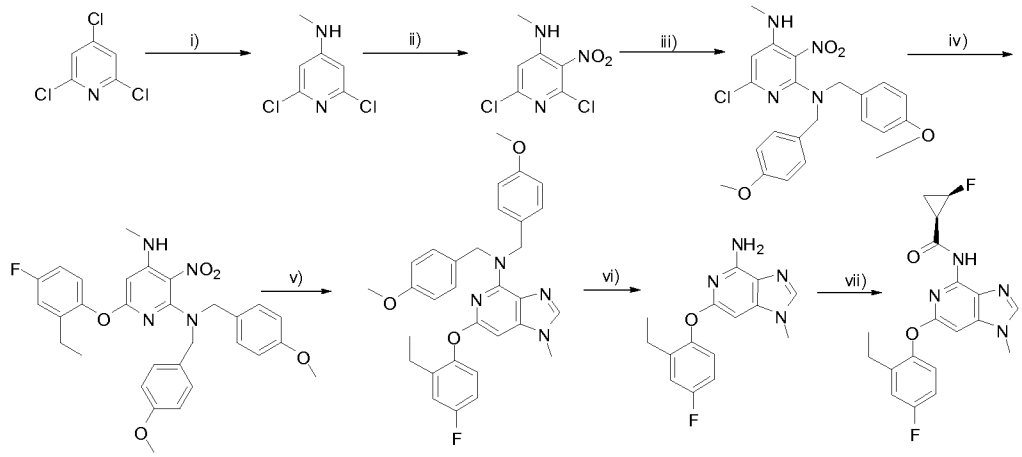
3.67.1. Step i : Cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0474] To a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-benzonitrile (1.0 eq, 200 mg) and pyridine in DCM (5 mL) is added cyclopropane carbonyl chloride (1.2 eq, 65 µL) and the resulting mixture is stirred at room temperature for 1 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by silica chromatography (EP/EA: 100/0 to 0/100, followed by EA/MeOH: 100/0 to 95/58) to yield the desired product.

3.67.2. Step ii): 3-ethyl-5-fluoro-4-((4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)benzamide

[0475] To a solution of cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (1.0 eq, 130 mg) in EtOH (4.0 mL) and DMSO (1.0 mL) is added a solution of 1N NaOH (500 µL) and a 35 % aqueous solution of H_2O_2 (400 µL). The resulting mixture is stirred at 50 °C for 1h. The volatiles are removed *in vacuo* and the residue is diluted in DCM and washed with a saturated solution of $NaHCO_3$. The organic layer is filtered through a phase separator and concentrated. The product is purified by silica chromatography (Petroleum eher/EtOAc: 100/0 to 0/100, followed by EtOAc/MeOH: 100/0 to 95/5).

3.68. Compound 69: (1R,2R)-N-(6-(2-ethyl-4-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.68.1. Step i: 2,6-dichloro-N-methylpyridin-4-amine

[0476] 33% v/v $MeNH_2$ solution in EtOH (101 mL) is added dropwise to a suspension of 2,4,6-trichloropyridine (25 g) in EtOH (25 mL). The mixture is stirred at room temperature for 24 h. The mixture is concentrated and the residue is treated with DIPE. The precipitated desired product is filtered off and dried under vacuum.

3.68.2. Step ii: 2,6-dichloro-N-methyl-3-nitropyridin-4-amine

[0477] 2,6-dichloro-N-methylpyridin-4-amine (19.3 g) is added in portions to conc. H_2SO_4 (40 mL) at 0 °C. After 5 min fuming HNO_3 (19 mL) is added dropwise over 5 min at 0 °C. The mixture is stirred at 0 °C for 1 h. The mixture is poured in icy water and extracted with DCM. The organic layer is dried and concentrated. The residue is dissolved in precooled (0 °C) conc. H_2SO_4 (18 mL) and the mixture is stirred for 1.5 h at 0 °C. The mixture is poured in icy water and extracted with DCM. The organic layer is dried and concentrated. NMR analysis of the residue revealed incomplete conversion. The residue is dissolved again in conc. H_2SO_4 (40 mL) and the mixture is stirred for 4 h at room temperature. The mixture is poured in icy water and extracted with DCM. The organic layer is dried and concentrated. The residue is triturated with petroleum ether to yield the desired product.

3.68.3. Step iii: 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine

[0478] Et_3N (3.5 mL, 1.1 eq) is added to a solution of $NH(PMB)_2$ (5.8 g, 1 eq) and 2,6-dichloro-N-methyl-3-nitropyridin-4-amine (5 g, 1 eq) in 1,4-dioxane (15 mL). The mixture is stirred at room temperature for 1 h and at 90 °C for 18 h. The mixture is diluted (DCM), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated to yield the desired product.

3.68.4. Step iv: 6-(2-ethyl-4-fluorophenoxy)-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine

[0479] A mixture of 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (300 mg, 1 eq), 2-ethyl-4-fluorophenol (140 mg, 1.5 eq) and Cs_2CO_3 (326 mg, 1.5 eq) in DMF (3 mL) is stirred at 80 °C for 2 h. Subsequently a mixture of 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.5 g, 1 eq), 2-ethyl-4-fluorophenol (711 mg, 1.5 eq) and Cs_2CO_3 (1.66 g,

1.5 eq) in DMF (12 mL) and a mixture of 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.5 g, 1 eq), 2-ethyl-4-fluorophenol (711 mg, 1.5 eq) and Cs_2CO_3 (1.66 g, 1.5 eq) in DMA (12 mL) are stirred at 80 °C for 19 h. Water is added to all mixtures and the two first mixtures are combined. Sat. NH_4Cl is added to both mixtures. The solid materials are filtered off, dissolved in acetone and the solutions are combined and concentrated. The residue is dissolved in ethyl acetate and the organic solution is washed (H_2O), dried (Na_2SO_4) and concentrated to yield the desired product.

3.68.5. Step v: 6-(2-ethyl-4-fluorophenoxy)-N,N-bis(4-methoxybenzyl)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine

[0480] A mixture of 6-(2-ethyl-4-fluorophenoxy)-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.7 g, 1 eq), Zn (2.03 g, 10 eq), p-TsOH.H_2O (1.8 g, 3 eq) and NH_4Cl (catalytic amount) in MeOH (12 mL) and $HC(OMe)_3$ (19 mL) is stirred at 40 °C for 2 h. LC-MS analysis revealed incomplete conversion. The mixture is filtered, concentrated and dissolved in $HC(OMe)_3$ (40 mL). The mixture is stirred at 110 °C for 17 h. The mixture is concentrated, diluted (DCM/MeOH) and filtered off. The residual solid is dissolved (DCM/acetone), washed (6 N NaOH) and the organic solution is dried (filtered through phase separator). The filtrate and the organic solution are combined and concentrated. The residue is purified by flash column chromatography (SiO_2, 10:90 to 35:65 ethyl acetate/petroleum ether) to yield the desired product.

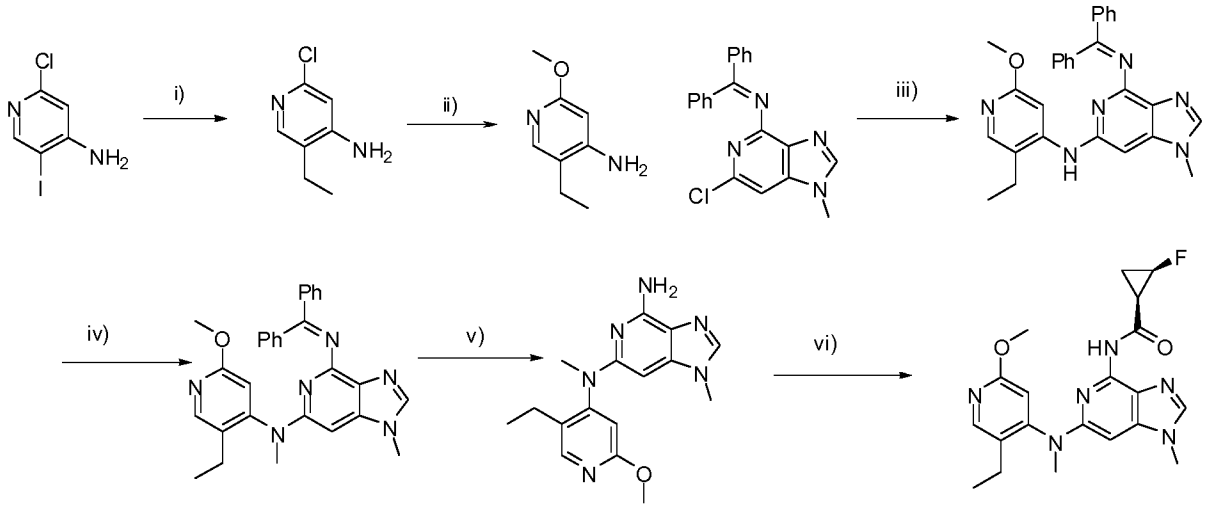
3.68.6. Step vi: 6-(2-ethyl-4-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine

[0481] A mixture of 6-(2-ethyl-4-fluorophenoxy)-N,N-bis(4-methoxybenzyl)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine (400 mg) in TFA is stirred at 50 °C for 2 h. The mixture is concentrated. The residue is purified by flash column chromatography (SiO_2, 50:50 to 100:0 ethyl acetate/petroleum ether) to yield the desired product.

3.68.7. Step vii: (1R,2R)-N-(6-(2-ethyl-4-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0482] A mixture of $(COCl)_2$ (0.13 mL, 2 eq), (R,R)-2-fluoro-cyclopropanecarboxylic acid (158 mg, 2 eq) and DMF (2 drops) in DCM (3 mL) is stirred at 0 °C for 30 min. A solution of 6-(2-ethyl-4-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine (100 mg, 1 eq) in DCM (3 mL) and pyridine (0.122 mL, 2 eq) are added in this order. The mixture is left to stir at room temperature for 15.5 h. The mixture is diluted (ethyl acetate), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated. The mixture is purified by flash column chromatography (SiO_2, 20:80 to 100:0 EtOAc/petroleum ether) and subsequently by preparative HPLC to yield the desired product.

3.69. Compound 70: (1R,2R)-N-(6-((5-ethyl-2-methoxypyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide.



3.69.1. Step i : 2-chloro-5-ethyl-4-pyridinamine

[0483] A round flask is charged with $PdCl_2$dppf DCM complex (0.32 g, 0.39 mmol, 0.1 eq) and Cs_2CO_3 (7.7 g, 23.64 mmol, 6.0 eq) and degassed with nitrogen. 2-Chloro-5-iodo-4-pyridinamine (1.0 g, 3.94 mmol, 1.0 eq), Et_3B 1M in hexane (5.12 mL, 5.12 mmol, 1.3 eq) are added, and the reaction is stirred at 55°C overnight. The reaction is filtered through celite and washed the solid pad with ethyl acetate. The organic layer is washed with water, dried over Na_2SO_4, filtered and removed under vacuum. The residue is purified by silica chromatography (EtOAc/pet. ether 40-60; from 0-50%) to give the desired product.

3.69.2. Step ii : 5-ethyl-2-methoxy-4-pyridinamine

[0484] 2-chloro-5-ethyl-4-pyridinamine (0.3 g, 1.92 mmol, 1.0 eq), copper iodide (Cat), sodium methoxide (0.52 g, 9.60 mmol, 5.0 eq) are dissolved in MeOH (2 mL), sealed in a microwave vial, and purged under nitrogen. The reaction is stirred at 160°C overnight. The reaction mixture is filtered through celite and the solid pad washed with MeOH. The solvent is removed under vacuum. The residue is purified by silica chromatography (EtOAc/pet. ether 40-60; from 0-100%) to give the desired product.

3.69.3. Step iii: N4-(diphenylmethylene)-N6-(5-ethyl-2-methoxypyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0485] A microwave vial is charged with 5-ethyl-2-methoxy-4-pyridinamine (110 mg, 0.72 mmol, 1.0 eq), 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine (250 mg, 0.72 mmol, 1.0 eq), the Cs_2CO_3 (586 mg, 1.80 mmol, 2.5 eq) and toluene (7 mL). The mixture is purged with nitrogen. $Pd_2(dba)_3$ (64 mg, 0.07 mmol, 0.1 eq) and XPhos (105 mg, 0.22 mmol, 0.3 eq) are added, and the reaction is stirred at 130°C overnight. The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60, from 50-100%; followed by MeOH/ethyl acetate, from 0-10%) to give the desired product.

3.69.4. Step iv: N4-(diphenylmethylene)-N6-(5-ethyl-2-methoxypyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0486] To a mixture of N4-(diphenylmethylene)-N6-(5-ethyl-2-methoxypyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (191 mg, 0.41 mmol, 1.0 eq) in THF (7 mL) at 0°C, it is added the NaH (49 mg, 1.23 mmol, 3.0 eq). After 30 min it is added iodomethane (77 µL, 1.23 mmol, 3.0 eq) and then the reaction is allowed to warm to room temperature for 2h. The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum to afford the desired compound.

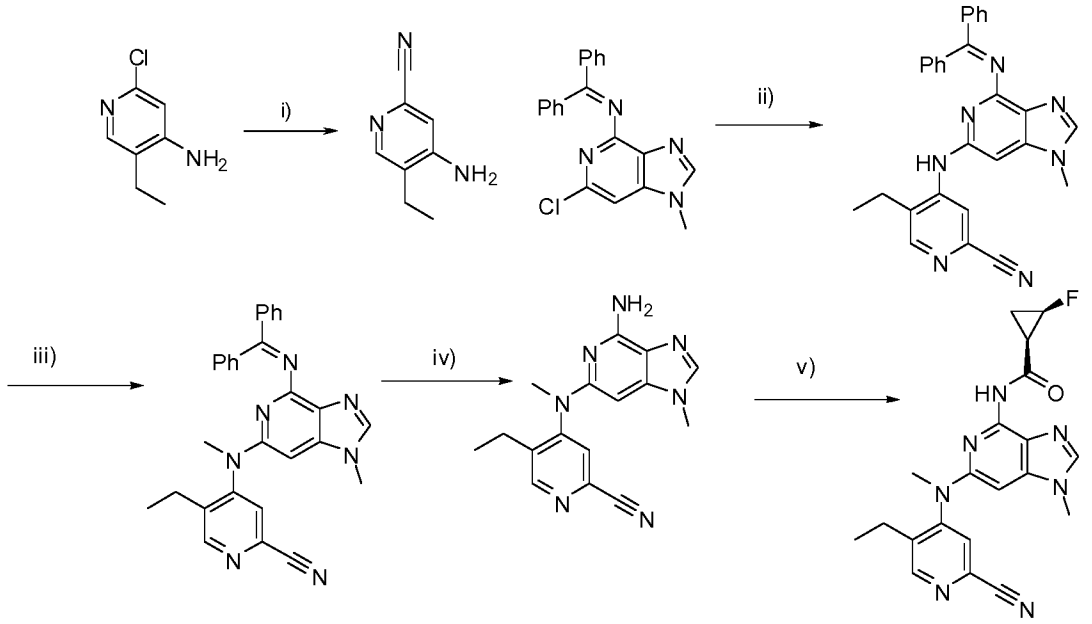
3.69.5. Step v: N6-(5-ethyl-2-methoxypyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0487] N4-(diphenylmethylene)-N6-(5-ethyl-2-methoxypyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (197 mg, 0.41 mmol, 1.0 eq) is dissolved in THF (2 mL), and a HCl 1M solution (2 mL) is added. The reaction is stirred at room temperature for 1h. The mixture is diluted with water and ethyl acetate. The aqueous layer is basified with a solution of NaOH 1N and the compound is extracted with DCM. The organic layer is filtered through a phase separator and concentrated to afford the desired compound.

3.69.6. Step vi: (1R,2R)-N-(6-((5-ethyl-2-methoxypyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0488] To a mixture of (1R,2R)-2-fluorocyclopropanecarboxylic acid (85 mg, 0.82 mmol, 2.0 eq) in DCM (2 mL) is added oxalyl chloride (71 µL, 0.82 mmol, 1.8 eq) and stirred at 0°C. 2 drops of 10% DMF solution in DCM are added. The reaction is stirred for 30 min. A solution of N6-(5-ethyl-2-methoxypyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (128 mg, 0.41 mmol, 1.0 eq) in DCM (2 mL) is added drop wise to the reaction mixture at 0°C, followed by the addition of pyridine (66 µL, 0.82 mmol, 2.0 eq) drop wise. The reaction stirred for 2h at room temperature. The reaction is diluted with DCM and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum and purified by preparative LC-MS to obtain the desired compound

3.70. Compound 71: (1R,2R)-N-(6-((2-cyano-5-ethylpyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.70.1. Step i: 2-cyano-5-ethyl-4-pyridinamine

[0489] 2-chloro-5-ethyl-4-pyridinamine (400 mg, 2.56 mmol, 1.0 eq), $Zn(CN)_2$ (477 mg, 4.06 mmol, 1.6 eq), and $PdCl_2$dppf DCM complex (212 mg, 0.26 mmol, 0.1 eq) are dissolved in dry dimethylacetamide (8 mL) and purged with nitrogen. The reaction is subjected to microwave conditions (T: 140°C, t: 3h). The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60; from 0-100%) to give the desired product as a dark green solid.

3.70.2. Step ii: 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethylpicolinonitrile

[0490] Prepared following step iii) for the synthesis of copound 70, starting from 2-cyano-5-ethyl-4-pyridinamine and 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine and 2-cyano-5-ethyl-4-pyridinamine.

3.70.3. Step iii): 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethylpicolinonitrile

[0491] Prepared following step iv) for the synthesis of compound 70, starting from 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethylpicolinonitrile.

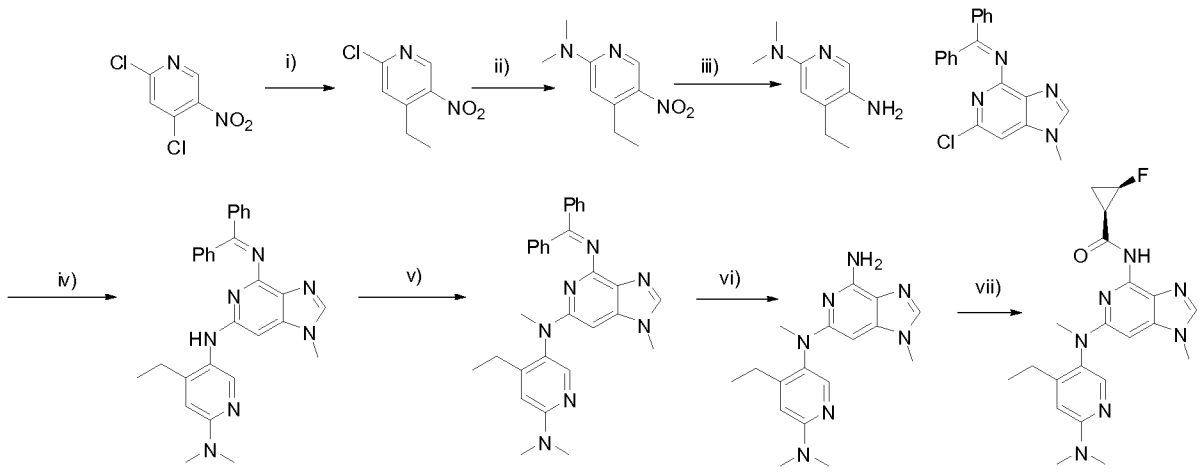
3.70.4. Step iv): 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethylpicolinonitrile

[0492] Prepared following step v) for the synthesis of compound 70 starting from 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl picolinonitrile.

3.70.5. Step v): (1R,2R)-N-(6-((2-cyano-5-ethylpyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0493] Prepared following step vi) for the synthesis of Compound 70, starting from 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethylpicolinonitrile.

3.71. Compound 72: (1R,2R)-N-(6-((6-(Dimethylamino)-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.71.1. Step i): 2-Chloro-4-ethyl-5-nitropyridine

[0494] 2,3-dichloro-5-nitropyridine (10.0 g, 52.0 mmol, 1.0 eq), ethylboronic acid (4.2 g, 57.8 mmol, 1.11 eq), $PdCl_2$dppf DCM complex (1.64 g, 2.08 mmol, 0.04 eq), and sodium carbonate (6.4 g, 60.84 mmol, 1.17 eq) are dissolved in a mixture of toluene/heptanes/water (7:3:4) (140 mL) and purged with nitrogen. The reaction is stirred at 85°C overnight. The reaction is diluted with DCM and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60; from 0-40%) to give the desired product.

3.71.2. Step ii): 2-Dimethylamine-4-ethyl-5-nitropyridine

[0495] 2-chloro-4-ethyl-5-nitropyridine (350 mg, 1.88 mmol, 1.0 eq) is dissolved in dimethylamine 5.6M in EtOH (3 mL). The reaction is stirred at room temperature for 5 min. The solvent is removed under vacuum to afford the desired compound.

3.71.3. Step iii): 3-Amino-2-dimethylamine-4-ethylpyridine

[0496] Into a microwave vial 2-dimethylamine-4-ethyl-5-nitropyridine (367 mg, 1.88 mmol, 1.0 eq) and zinc metal (1.23 g, 18.8 mmol, 10 eq) are suspended in MeOH (2 mL). To the suspension are added formic acid (0.4 mL) and a spatula of NH_4Cl. The vial is sealed and stirred at 80°C for 1 h. The reaction mixture is filtered, and the solid pad is washed with MeOH. The solvent of the filtrate is removed under vacuum to afford the desired compound.

3.71.4. Step iv): N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N4-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0497] A microwave vial is charged with 3-amino-2-dimethylamine-4-ethylpyridine (187 mg, 1.13 mmol, 1.1 eq), 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine (356 mg, 1.03 mmol, 1.0 eq), the Cs_2CO_3 (1.51 g, 4.63 mmol, 4.5 eq) and dioxane (5 mL). The mixture is purged with nitrogen. Palladium (II) acetate (45 mg, 0.21 mmol, 0.2 eq) and BINAP (193 mg, 0.31 mmol, 0.3 eq) are added, and the reaction is stirred at 110°C overnight. The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60, from 0-100%) to give the desired product.

3.71.5. Step v): N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N4-(diphenylmethylene)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0498] Prepared following step iv) for the synthesis of compound 70, starting from N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N4-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

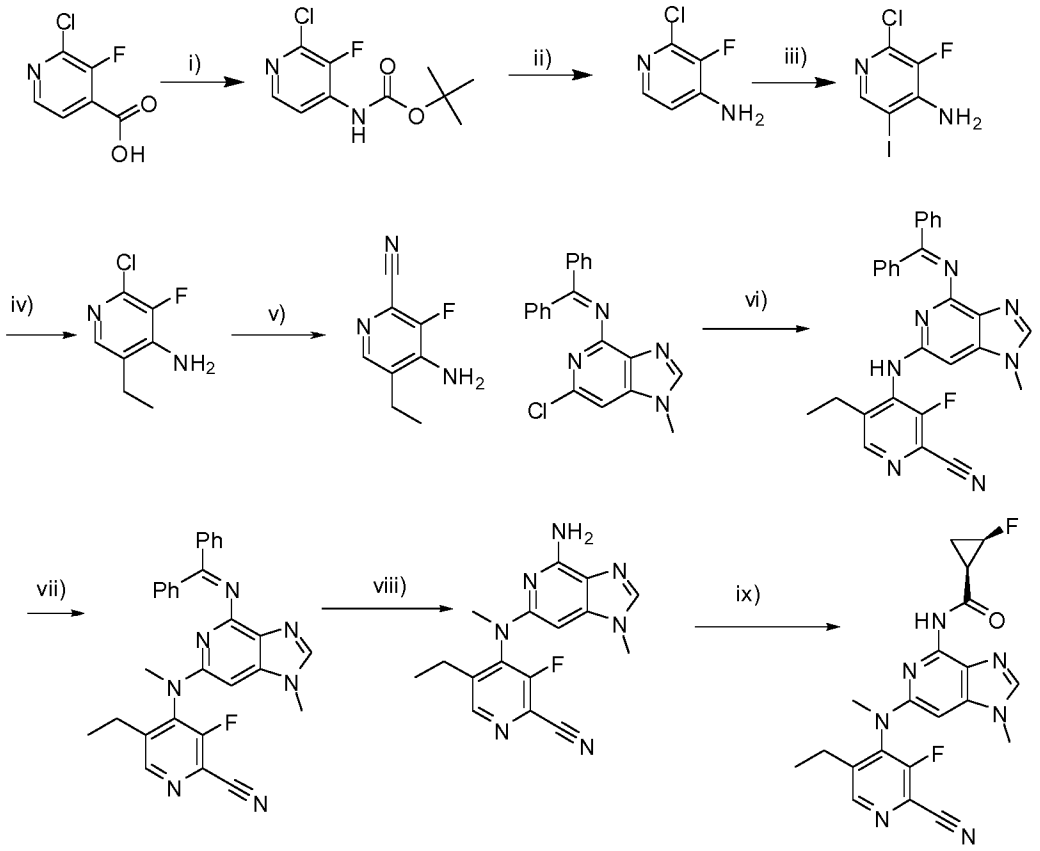
3.71.6. Step vi: N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0499] Prepared following step v) for the synthesis of compound 70, starting from N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N4-(diphenylmethylene)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.71.7. Step vii: (1R,2R)-N-(6-((6-(dimethylamino)-4-ethylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0500] Prepared following step vi) for the synthesis of compound 70, starting from N6-(6-(dimethylamino)-4-ethylpyridin-3-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.72. Compound 73: (1R,2R)-N-(6-((2-Cyano-5-ethyl-3-fluoropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.72.1. Step i: Carbamic acid, N-(2-chloro-3-fluoro-4-pyridinyl)-1,1-dimethylethyl ester

[0501] To a mixture of 2-chloro-3-fluoronicotinic acid (3.55 g, 20.2 mmol, 1.0 eq), TEA (8.4 mL, 60.6 mmol, 3.0 eq) in a mixture of dry toluene (40 mL) and dry ^{t}BuOH (40 mL) under nitrogen, is added diphenylphosphoryl azide (DPPA) (6.51 mL, 30.1 mmol, 1.5 eq). The reaction is heated to 110°C for 2 h. The reaction is diluted with water and the compound is extracted with DCM. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/DCM, from 0-20% in 15CV) to give the desired product as transparent oil.

3.72.2. Step ii): 2-chloro-3-fluoro-4-aminopyridine

[0502] To a mixture of carbamic acid, N-(2-chloro-3-fluoro-4-pyridinyl)-1,1-dimethylethyl ester (4.97 g, 20.2 mmol, 1.0 eq) in DCM (30 mL), it is added TFA (15 mL), and the reaction is stirred at room temperature for 3 h. The solvent of the reaction is removed under vacuum. The residue is purified by silica chromatography (10% 7N NH_3 MeOH in DCM/DCM, from 0-100%) to afford the desired compound as a white powder.

3.72.3. Step iii): 2-chloro-3-fluoro-5-iodine-4-aminopyridine

[0503] To a solution of iodine (5.13 g, 20.2 mmol, 1.0 eq) in EtOH (50 mL) is added silver sulphate (6.30 g, 20.2 mmol, 1.0 eq) and 2-chloro-3-fluoro-4-aminopyridine (2.95 g, 20.2 mmol, 1.0 eq). The reaction stirred at 50°C for 16 h. The reaction mixture is filtered and the solvent is evaporated. The

residue is diluted in DCM, washed with aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and the solvent is removed under vacuum to afford the desired compound as a pale brown solid.

3.72.4. Step iv): 2-chloro-5-ethyl-3-fluoro-4-aminopyridine

[0504] The $PdCl_2$dppf complex with DCM (2.48 g, 3.04 mmol, 0.2 eq) and Cs_2CO_3 (14.89 g, 45.69 mmol, 3.0 eq) are added in a round bottom flask and degassed under nitrogen. 2-Chloro-3-fluoro-5-iodine-4-aminopyridine (4.14 g, 15.23 mmol, 1.0 eq) and triethylborane (1M in hexane) (20.0 mL, 20.0 mmol, 1.3 eq) are added and the reaction is stirred at 55°C for 20h. The reaction is filtered through celite and washed the solid pad with ethyl acetate. The organic layer is washed with water. The organic layer is dried over Na_2SO_4, filtered and removed under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60, from 10-50%) to afford the desired compound.

3.72.5. Step v): 2-cyano-5-ethyl-3-fluoro-4-aminopyridine

[0505] A mixture of 2-chloro-5-ethyl-3-fluoro-4-aminopyridine (323 mg, 1.86 mmol, 1.0 eq), zinc (II) cyanide (423 mg, 3.71 mmol, 1.6 eq), $PdCl_2$dppf complex with DCM (200 mg, 0.23 mmol, 0.1 eq) in DMA dried with pre-activated molecular sieves (10 mL), is purged with nitrogen and subjected to microwave conditions (T: 120°C; t: 4h). The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over Na_2SO_4, filtered and removed the solvent under vacuum. The residue is purified by silica chromatography (ethyl acetate/pet. ether 40-60, from 0-100%) to afford the desired compound.

3.72.6. Step vi): 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethyl-3-fluoropicolinonitrile

[0506] Prepared following step iv) for the synthesis of compound 72 starting from 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine and 2-cyano-5-ethyl-3-fluoro-4-aminopyridine.

3.72.7. Step vii): 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-3-fluoropicolinonitrile.

[0507] Prepared following step iv) for the synthesis of compound 70, starting from 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethyl-3-fluoropicolinonitrile.

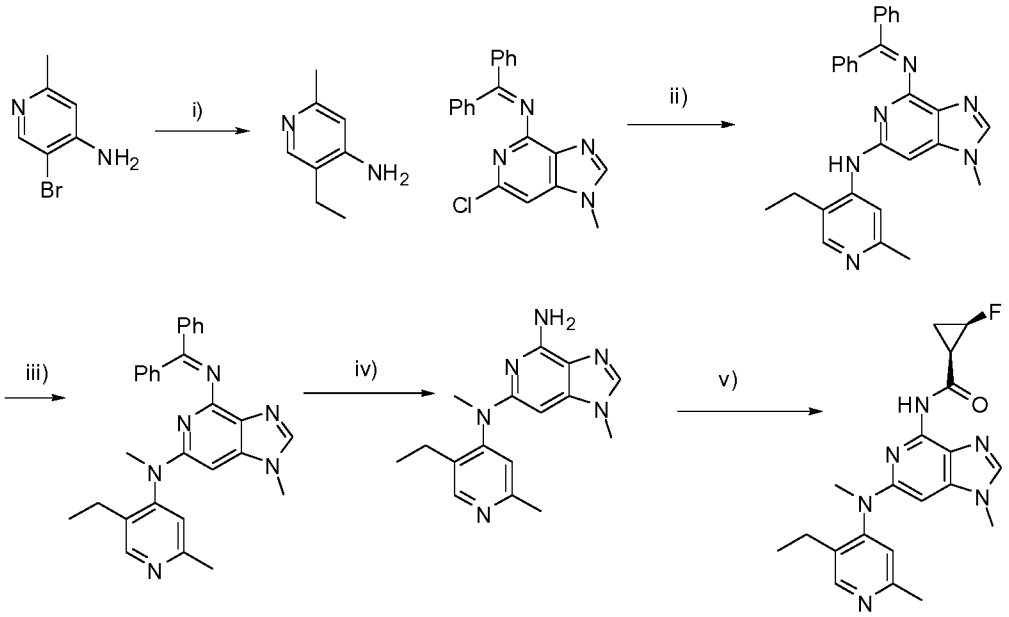
3.72.8. Step viii): 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-3-fluoropicolinonitrile.

[0508] Prepared following step v) for the synthesis of compound 70, starting from 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-3-fluoropicolinonitrile.

3.72.9. Step ix): (1R,2R)-N-(6-((2-cyano-5-ethyl-3-fluoropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide.

[0509] Prepared following step vi) for the synthesis of compound 70, starting from 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-3-fluoropicolinonitrile.

3.73. Compound 74: (1R,2R)-N-(6-((5-ethyl-2-methylpyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide.



3.73.1. Step i): 5-Ethyl-2-methyl-4-aminopyridine

[0510] Prepared following step i) for the synthesis of compound 70, starting from 5-bromo-2-methyl-4-aminopyridine.

3.73.2. Step ii): N4-(diphenylmethylene)-N6-(5-ethyl-2-methylpyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0511] Prepared following step iv) for the synthesis of compound 72, starting from 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine and ethyl-2-methyl-4-aminopyridine.

3.73.3. Step iii): N4-(diphenylmethylene)-N6-(5-ethyl-2-methylpyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0512] Prepared following step iv) for the synthesis of Compound 70, starting from N4-(diphenylmethylene)-N6-(5-ethyl-2-methylpyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

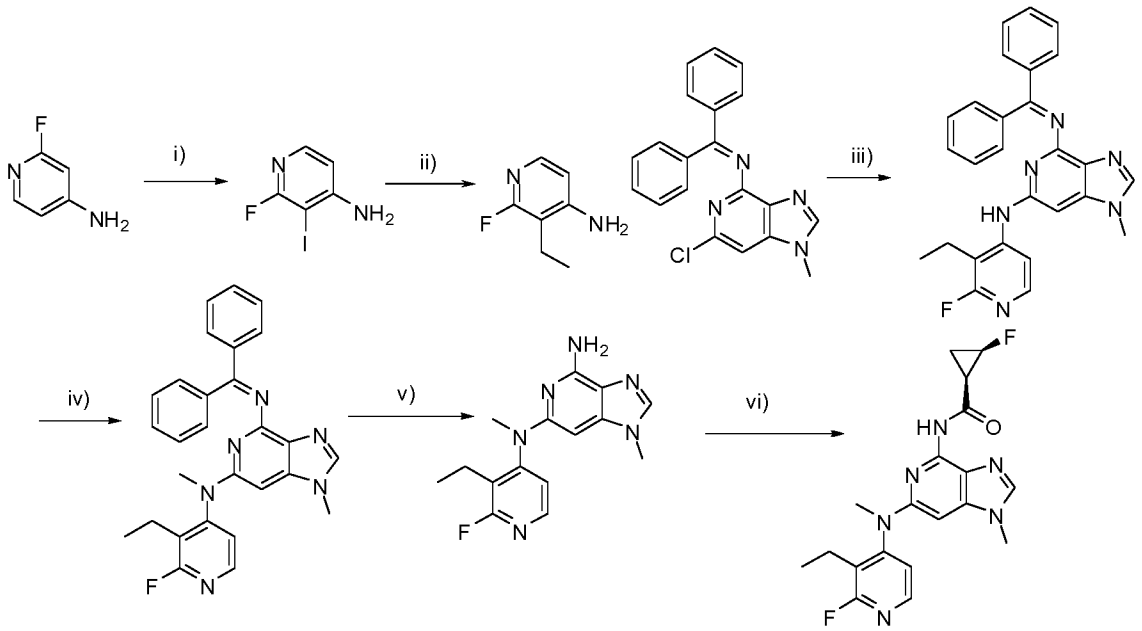
3.73.4. Step iv): N6-(5-ethyl-2-methylpyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0513] Prepared following step v) for the synthesis of Compound 70, starting from N4-(diphenylmethylene)-N6-(5-ethyl-2-methylpyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.73.5. Step v): (1R,2R)-N-(6-((5-ethyl-2-methylpyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0514] Prepared following step vi) for the synthesis of Compound 70, starting from N6-(5-ethyl-2-methylpyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.74. Compound 75: (1R,2R)-N-(6-((3-ethyl-2-fluoropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.74.1. Step i: 2-Fluoro-3-iodo-4-aminopyridine

[0515] To a solution of iodine (1.13 g, 4.46 mmol, 1.0 eq) in EtOH (10 mL) is added silver sulphate (1.39 g, 4.46 mmol, 1.0 eq) and 2-fluoro-4aminopyridine, and the reaction is stirred at room temperature overnight. The reaction mixture is filtered and the solvent is evaporated. The residue is diluted in DCM, extracted with saturated aqueous $Na_2S_2O_3$ solution, dried over Na_2SO_4, and the solvent is removed under vacuum to afford the desired compound.

3.74.2. Step ii: 3-Ethyl-2-fluoro -4-aminopyridine

[0516] Prepared following step i) for the synthesis of compound 70, starting from 2-fluoro-3-iodo-4-aminopyridine.

3.74.3. Step iii: N4-(diphenylmethylene)-N6-(3-ethyl-2-fluoropyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

[0517] Prepared following step iv) for the synthesis of Compound 72, starting from 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine and 3-ethyl-2-fluoro-4-aminopyridine.

3.74.4. Step iv: N4-(diphenylmethylene)-N6-(3-ethyl-2-fluoropyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

[0518] Prepared following step iv) for the synthesis of compound 70, starting from N4-(diphenylmethylene)-N6-(3-ethyl-2-fluoropyridin-4-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

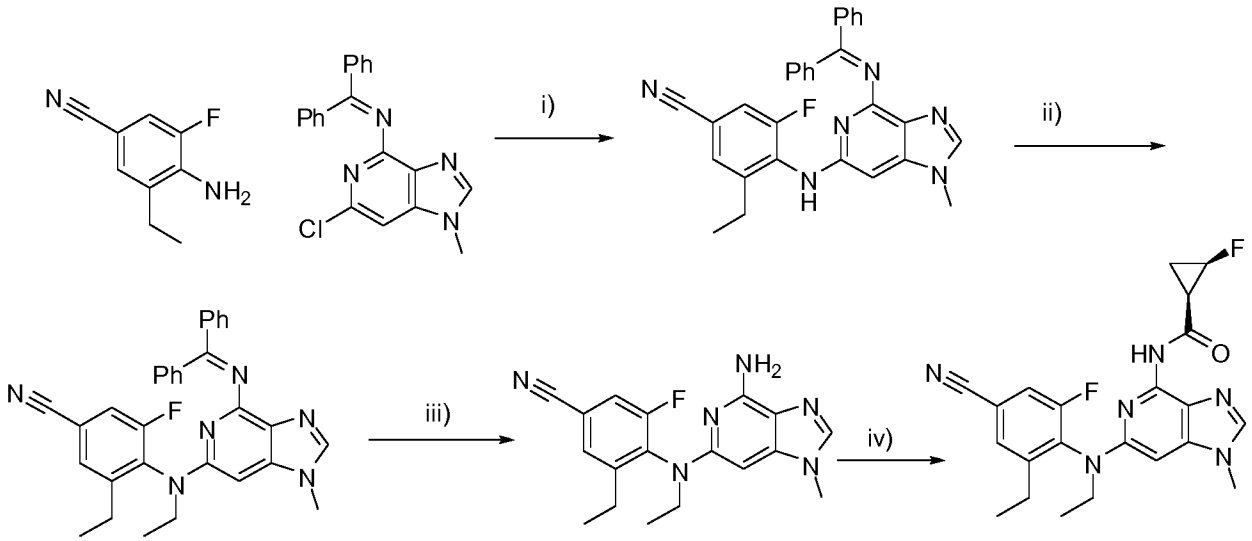
3.74.5. Step v: N6-(3-ethyl-2-fluoropyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

[0519] Prepared following step v) for the synthesis of compound 70, starting from N4-(diphenylmethylene)-N6-(3-ethyl-2-fluoropyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.74.6. Step vi: (1R,2R)-N-(6-((3-ethyl-2-fluoropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide.

[0520] Prepared following step vi) for the synthesis of compound 70, starting from N6-(3-ethyl-2-fluoropyridin-4-yl)-N6,1-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.75. Compound 76: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.75.1. Step i: 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzonitrile.

[0521] Prepared following step iii) for the synthesis of compound 70, starting from 4-cyano-2-ethyl-5-fluoroaniline and 6-chloro-*N*-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine.

3.75.2. Step ii: 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-ethyl-amino}-3-ethyl-5-fluoro-benzonitrile

[0522] Prepared following step iv) for the synthesis of compound 70, starting from 4-[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzonitrile and iodoethane as alkylating agent.

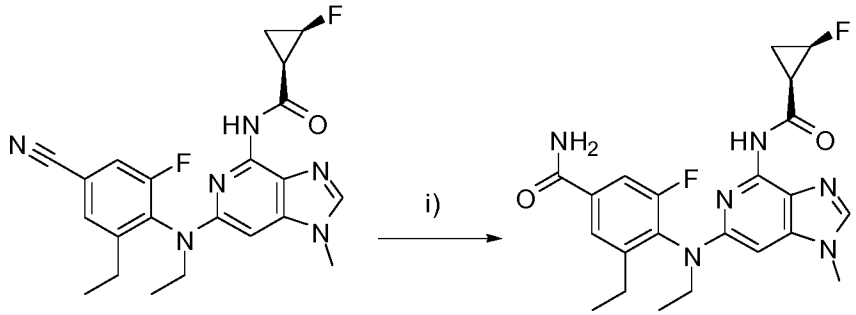
3.75.3. Step iii: 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-ethyl-amino]-3-ethyl-5-fluoro-benzonitrile

[0523] Prepared following step v) for the synthesis of compound 70, starting from 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-ethyl-amino}-3-ethyl-5-fluoro-benzonitrile.

3.75.4. Step iv: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0524] Prepared following step vi) for the synthesis of compound 70, starting from 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-ethyl-amino]-3-ethyl-5-fluoro-benzonitrile.

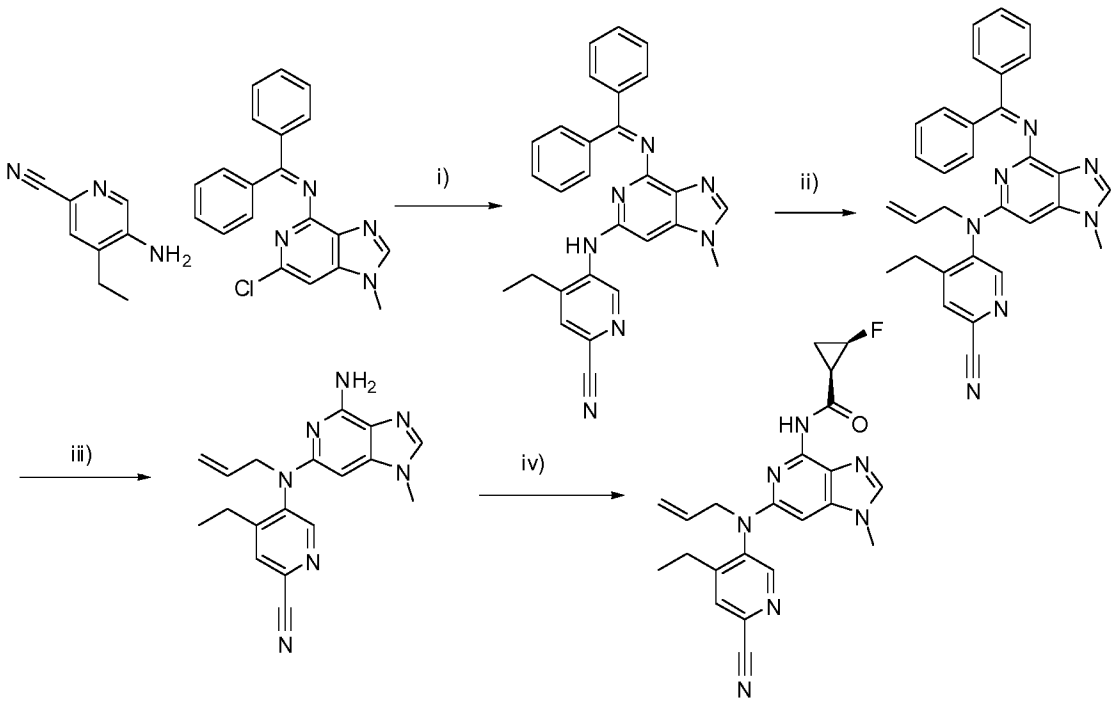
3.76. Compound 77: 3-Ethyl-4-(ethyl-{4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-amino)-5-fluoro-benzamide



3.76.1. Step i: 3-Ethyl-4-(ethyl-{4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-amino)-5-fluoro-benzamide

[0525] To a solution of (1*R*,2*R*)-2-fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethyl-6-fluoro-phenyl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (157 mg, 0.37 mmol, 1 eq.) in ethanol (1.0 mL) and DMSO (0.25 mL), it is added a solution of 1N NaOH (0.13 mL) and a 35 % aqueous solution of H_2O_2 (0.1 mL). The resulting mixture is stirred at 50°C for 2h. The compound is purified by SCX column and preparative LCMS.

3.77. Compound 78: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[allyl-(6-cyano-4-ethyl-pyridin-3-yl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.77.1. Step i: 5-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-4-ethyl-pyridine-2-carbonitrile

[0526] Prepared following step iii) for the synthesis of compound 70, starting from 5-Amino-4-ethyl-pyridine-2-carbonitrile and 6-chloro-*N*-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine.

3.77.2. Step ii: 5-{Allyl-[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-amino}-4-ethyl-pyridine-2-carbonitrile

[0527] Prepared following step iv) for the synthesis of compound 70, starting from 5-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-4-ethyl-pyridine-2-carbonitrile and allylbromide as alkylating agent.

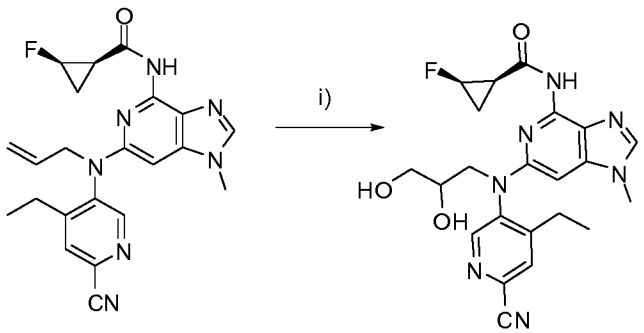
3.77.3. Step iii: 5-[Allyl-(4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-amino]-4-ethyl-pyridine-2-carbonitrile

[0528] Prepared following step v) for the synthesis of compound 70, starting from 5-{allyl-[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-amino}-4-ethyl-pyridine-2-carbonitrile.

3.77.4. Step iv: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[allyl-(6-cyano-4-ethyl-pyridin-3-yl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0529] Prepared following step vi) for the synthesis of compound 70, starting from 5-[Allyl-(4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-amino]-4-ethyl-pyridine-2-carbonitrile.

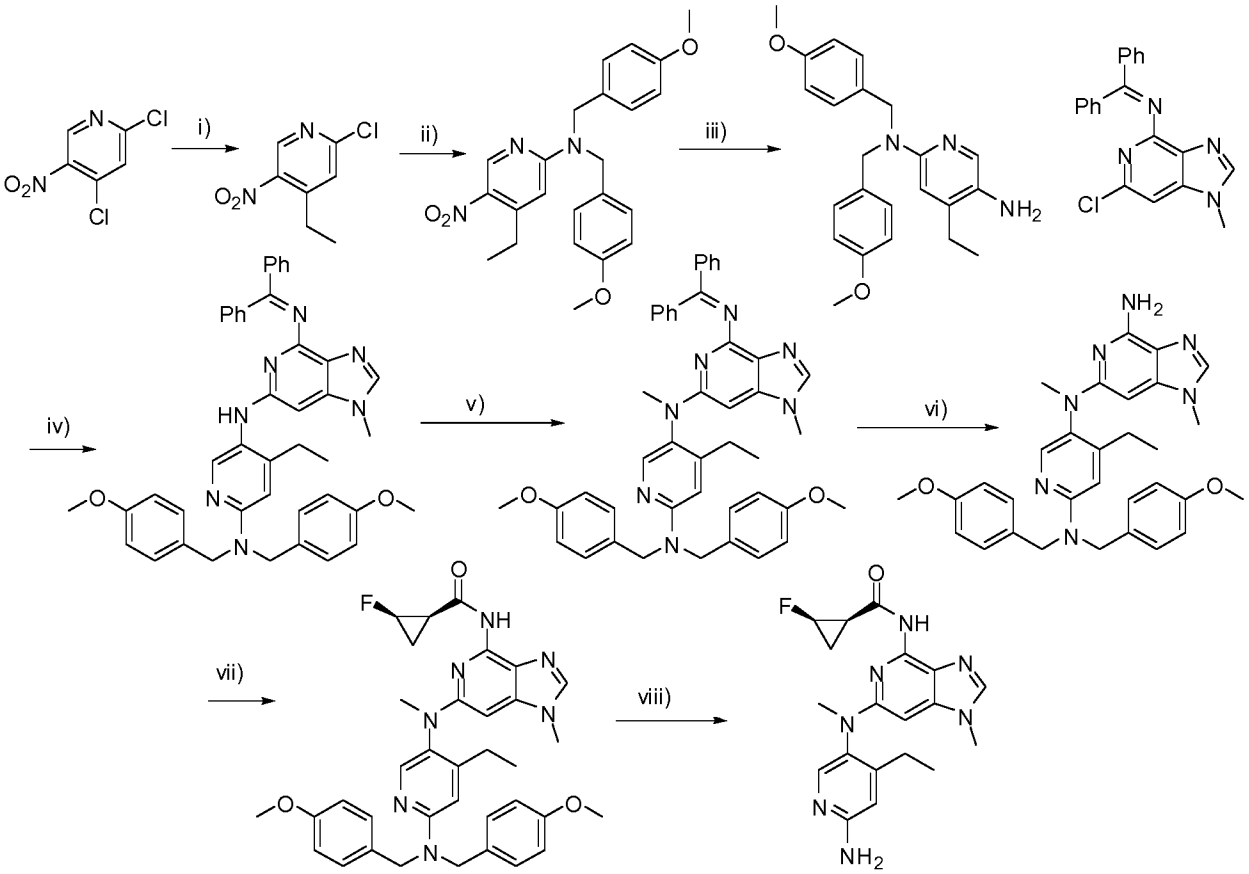
3.78. Compound 79: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-4-ethyl-pyridin-3-yl)-(2,3-dihydroxy-propyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.78.1. Step i: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-4-ethyl-pyridin-3-yl)-(2,3-dihydroxy-propyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide.

[0530] To a mixture of (1R,2R)-2-fluoro-cyclopropanecarboxylic acid {6-[allyl-(6-cyano-4-ethyl-pyridin-3-yl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide (146 mg, 0.35 mmol, 1.0 eq) in acetone (1.5 mL) and water (0.17 mL), it is added OsO_4 (0.3 mmol/g) (1.17 g, 0.35 mmol, 1.0 eq) and *N*-methylmorpholine-*N*-oxide (248 mg, 2.10 mmol, 6.0 eq) at rt. The mixture is stirred at 65°C for two days. The reaction is filtered and the solid pad washed with methanol. The filtrate is concentrated under vacuum. The mixture is diluted with ethyl acetate and washed with $NaHCO_3$. The organic layer is dried over Na_2SO_4, filtered, concentrated under *vacuum* and purified by preparative LCMS.

3.79. Compound 80: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-amino-4-ethylpyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.79.1. Step i: 2-Chloro-4-ethyl-5-nitropyridine

[0531] 2,4-Dichloro-5-nitropyridine (10g, 52.0 mmol, 1.0 eq), ethyl boronic acid (4.2 g, 57.8 mmol, 1.11 eq) and sodium carbonate (6.4 g, 60.84 mmol, 1.17 mmol) are dissolved in the ternary solvent system (toluene/heptane/water (7:3:4); 140 mL). The mixture is purged under nitrogen. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1.64 g, 2.08 mmol, 0.04 eq) is added and the reaction is stirred at 85°C during 15h. The reaction is diluted with DCM and washed with water. The organic layer is dried over sodium sulfate, filtered and removed the solvent under vacuum. The compound is purified over a pre-packed 80g silica flash chromatography (ethyl acetate/pet. ether 40-60, from 0-40% in 15CV) to afford the desired compound as a yellow oil.

3.80. Step ii: (4-Ethyl-5-nitropyridin-2-yl)-bis-(p-methoxybenzyl)amine

[0532] A solution of 2-chloro-4-ethyl-5-nitro-pyridine (1.0 g, 5.4 mmol, 1.0 eq), bis-(*p*-methoxybenzyl)amine (1.52 g, 5.9 mmol, 1.1 eq) and trimethylamine (1.13 mL, 8.1 mmol, 1.5 eq) in THF (15 mL) is stirred at 120°C for 3 days. The reaction is diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate, filtered and removed the solvent under vacuum to afford the desired compound.

3.80.1. Step iii: 4-Ethyl-N,N-bis-(p-methoxybenzyl)pyridine-2,5-diamine

[0533] A mixture of (4-ethyl-5-nitropyridin-2-yl)-bis-(*p*-methoxybenzyl)amine (2.20 g, 5.4 mmol, 1.0 eq), zinc powder (3.53 g, 54.0 mmol, 10 eq), ammonium chloride (small spatula, catalytically), formic acid (2 mL) in methanol (10 mL) is stirred at 80°C for 1h. The reaction is filtered through a metal "catcher paper", and the solid pad is washed with methanol. The solvent of the filtrate is removed under vacuum. The compound is purified by a pre-packed 50g silica flash chromatography (ethyl acetate/pet. ether 40-60, from 0-100% in 10CV; MeOH/ethyl acetate, from 0-10% in 10CV) to afford the desired compound.

3.80.2. Step iv: N4-Benzhydrylidene-N6-{6-[bis-(p-methoxybenzyl)-amino]-4-ethyl-pyridin-3-yl}-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0534] Prepared following step iii) for the synthesis of compound 70, starting 4-ethyl-N2,N2-bis-(*p*-methoxybenzyl)pyridine-2,5-diamine and 6-chloro-*N*-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine.

3.80.3. Step v: N4-Benzhydrylidene-N6-{6-[bis-(p-methoxybenzyl)-amino]-4-ethyl-pyridin-3-yl}-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine;

[0535] Prepared following step iv) for the synthesis of compound 70, starting from N4-Benzhydrylidene-N6-{6-[bis-(*p*-methoxybenzyl)-amino]-4-ethyl-pyridin-3-yl}-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine and iodomethane as alkylating agent.

3.80.4. Step vi: N6-{6-[Bis-(p-methoxybenzyl)-amino]-4-ethylpyridin-3-yl}-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0536] N4-Benzhydrylidene-N6-{6-[bis-(*p*-methoxybenzyl)-amino]-4-ethyl-pyridin-3-yl}-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (2.58 g, 3.61 mmol, 1.0 eq) is dissolved binary mixture of HCl 1M/THF (1:1; 20 mL), and the reaction is stirred at room temperature until completion. The mixture is diluted with water and ethyl acetate. The aqueous layer is then basified with a solution of NaOH 1N and extracted with DCM. The organic layer is dried over sodium sulfate, filtered and concentrated. The crude compound is left overnight under vacuum to afford the desired compound.

3.80.5. Step vii: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-({6-[bis-(p-methoxybenzyl)-amino]-4-ethyl-pyridin-3-yl}-methyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-amide

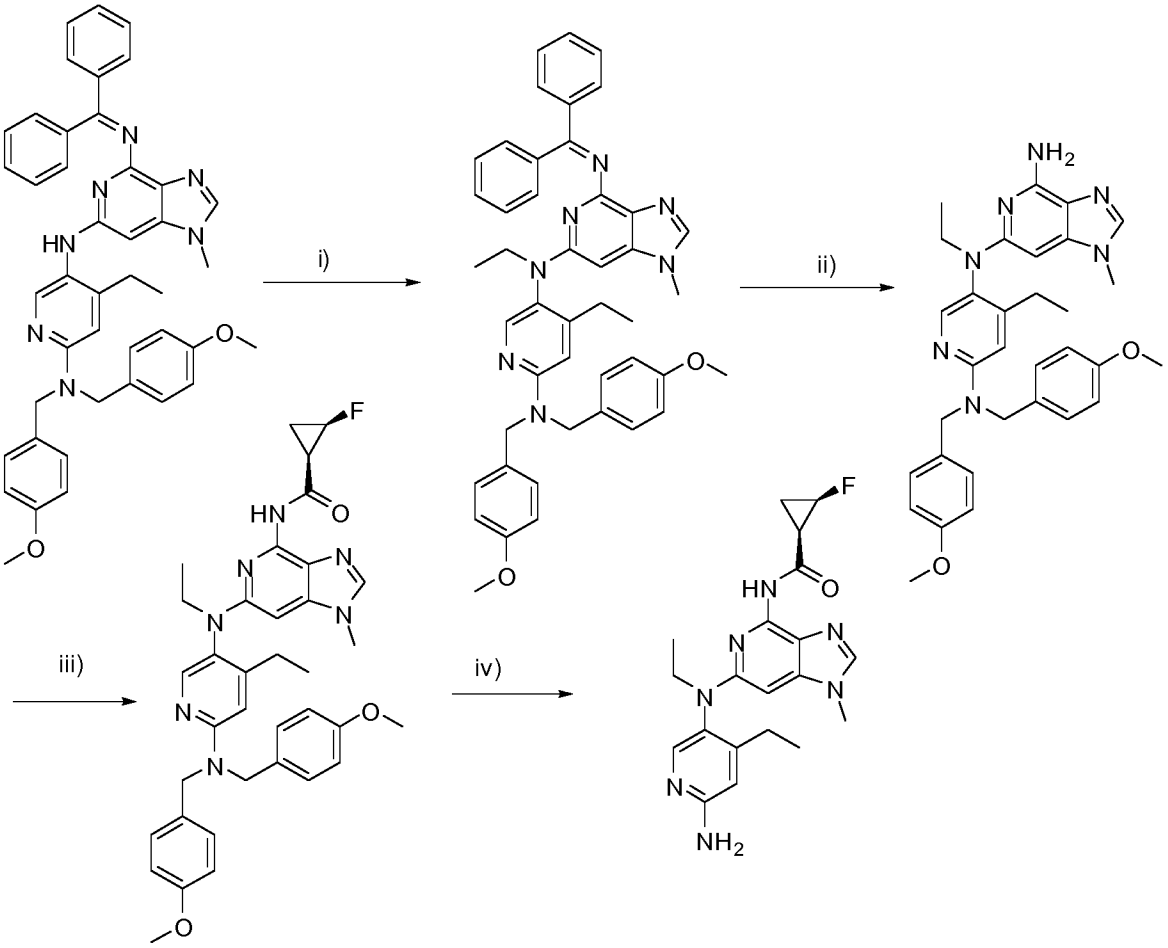
[0537] Prepared following step vi) for the synthesis of compound 70, starting from *N*6-{6-[bis-(*p*-methoxybenzyl)-amino]-4-ethylpyridin-3-yl}-1,*N*6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.80.6. Step viii: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-amino-4-ethylpyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0538] (1*R*,2*R*)-2-Fluoro-cyclopropanecarboxylic acid [6-({6-[bis-(*p*-methoxybenzyl)-amino]-4-ethylpyridin-3-yl}-methylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]amide (2.25 g, 3.61 mmol, 1.0 eq) is dissolved trifluoroacetic acid (10.0 mL) and the reaction is stirred at 85°C for 1.5h. The solvent of the reaction is removed under vacuum. The crude solid is redissolved with ethyl acetate and washed with

water. The organic layer is dried over sodium sulfate, filtered and removed the solvent under vacuum. The compound is purified by preparative UPLC to afford the desired compound.

3.81. Compound 81: (1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.81.1. Step i: N5-[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-N5,4-diethyl-N2,N2-bis[(4-methoxyphenyl)methyl]pyridine-2,5-diamine

[0539] Prepared following step iv) for the synthesis of compound 70, starting from N5-[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-4-ethyl-N2,N2-bis[(4-methoxyphenyl)methyl]pyridine-2,5-diamine and iodoethane as alkylating agent.

3.81.2. Step ii: N6-[6-[bis[(4-methoxyphenyl)methyl]amino]-4-ethyl-3-pyridyl]-N6-ethyl-1-methyl-imidazo[4,5-c]pyridine-4,6-diamine

[0540] N5-[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-N5,4-diethyl-N2,N2-bis[(4-methoxyphenyl)methyl]pyridine-2,5-diamine (286 mg, 0.40 mmol, 1.0 eq) is dissolved binary mixture of HCl 1M/THF (1:1; 10 mL), and the reaction is stirred at room temperature for 1h. The mixture is diluted with water and ethyl acetate. The aqueous layer is then basified with a solution of NaOH 1N and extracted with DCM. The organic layer is dried over sodium sulfate, filtered and concentrated. The crude compound is left overnight under vacuum to afford the desired compound.

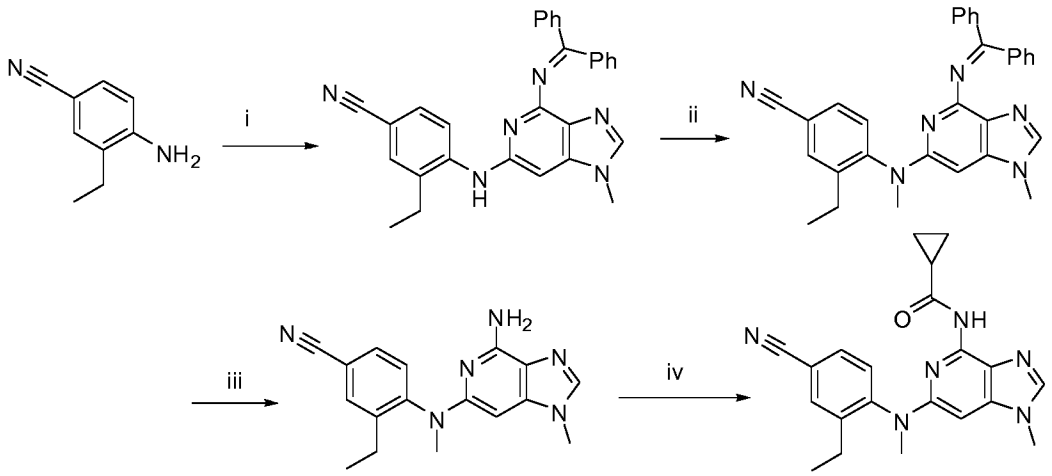
3.81.3. Step iii: (1R,2R)-N-[6-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-ethyl-3-pyridyl]-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0541] Prepared following step vi) for the synthesis of compound 70, starting from N6-[6-[bis[(4-methoxyphenyl)methyl]amino]-4-ethyl-3-pyridyl]-N6-ethyl-1-methyl-imidazo[4,5-c]pyridine-4,6-diamine.

3.81.4. Step iv: (1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0542] (1R,2R)-N-[6-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-ethyl-3-pyridyl]-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide (225 mg, 0.40 mmol, 1.0 eq) is dissolved in a binary solution of trifluoroacetic acid/DCM (1:1) (6.0 mL) and the reaction is stirred at 50°C for 4h. The solvent of the reaction is removed under vacuum. The crude solid is redissolved with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate, filtered and removed the solvent under vacuum. The compound is purified by preparative UPLC to afford the desired compound.

3.82. Compound 82: 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethyl-5-fluorobenzamide



3.82.1. Step i: 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-benzonitrile

[0543] A mixture of Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine (1.0 eq, 500 mg), 4-Amino-3-ethyl-benzonitrile (1.0 eq, 210 mg), and Cs_2CO_3 (2.5 eq, 1.2 g) in dry dioxane (7 mL) are charged in a round bottom flask and degassed under nitrogen flow. To this solution is added $Pd(OAc)_2$ (0.2 eq, 65 mg) and BINAP (0.3 eq, 270 mg) and the mixture is degassed again and then stirred at 100 °C for 16 h.

[0544] The mixture is diluted with DCM and filtered through a celite pad. Solids are thoroughly washed with DCM. The filtrate is washed with sat $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The residue is purified by silica chromatography (EP/EtOAc: 100/0 to 20/80) to afford the desired product.

3.82.2. Step ii: 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl- -benzonitrile

[0545] To a mixture of 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-benzonitrile (1.0 eq, 430 mg) and NaH (3.0 eq, 110 mg) in dry THF (15 mL) is added iodomethane (3.0 eq, 175 µL). The mixture is stirred at room temperature. After 1 h, the mixture is diluted with EtOAc and neutralized by addition of water. The organic layer is then washed with sat $NaHCO_3$, filtered through a phase separator and concentrated. The residue is used without further purification.

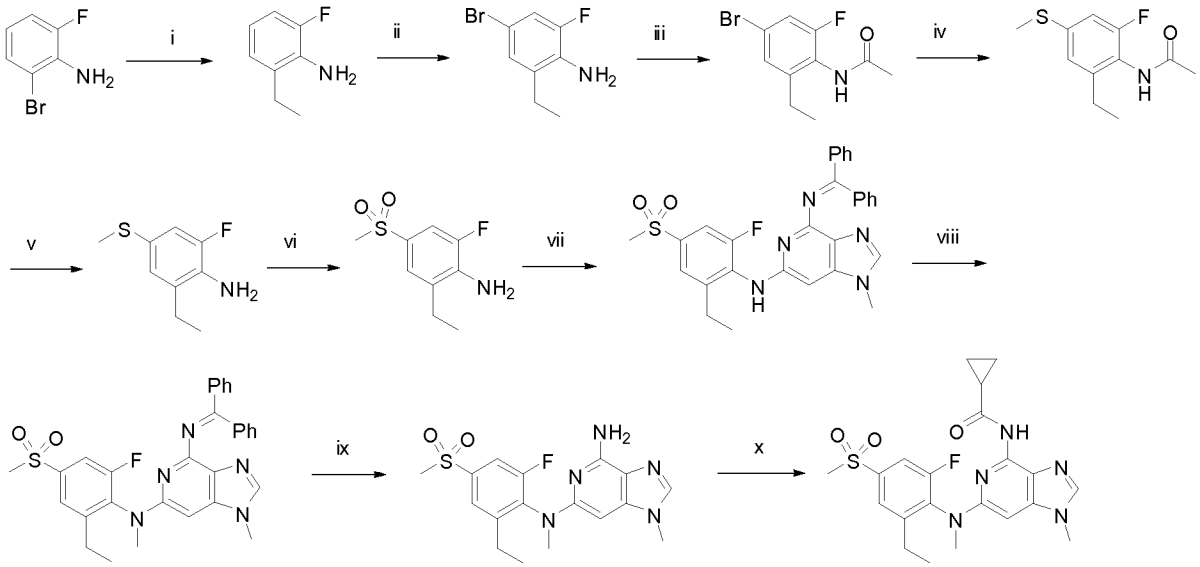
3.82.3. Step iii: 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-benzonitrile

[0546] To a mixture of 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-benzonitrile (1.0 eq, 490 mg) in dry THF (5 mL) is added an aqueous solution of hydrochloric acid (2.0 M, 5 mL) and the mixture is then stirred at room temperature for 30 min. The mixture is diluted with water and EtOAc. The organic layer is discarded. The aqueous layer is basified with a solution of NaOH 1N and extracted with DCM. The organic layer is filtered through a phase separator and concentrated. The residue is used in the next step without further purification.

3.82.4. Step iv : 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethyl-5-fluorobenzamide

[0547] To a solution of 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-benzonitrile (1.0 eq, 90 mg) and pyridine (2.0 eq, 45 µL) in DCM (3 mL) is added cyclopropane carbonyl chloride (1.2 eq, 35 µL) and the resulting mixture is stirred at room temperature for 1 h. The mixture is diluted with DCM and washed with a saturated solution of $NaHCO_3$, filtered through a phase separator and concentrated. The residue is purified by silica chromatography (EP/EA: 100/0 to 0/100, followed by EA/MeOH: 100/0 to 95/5) to yield the desired product.

3.83. Compound 83: N-(6-((2-ethyl-6-fluoro-4-(methylsulfonyl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.83.1. Step i : 2-Ethyl-6-fluoro-aniline

[0548] A mixture of 2-bromo-6-fluoroaniline (1.0 eq, 5,0 g), triethylborane (1.3 eq, 34.4 mL), and Cs_2CO_3 (3.0 eq, 25 g) in dry DMF (200 mL) are charged in a round bottom flask and degassed under nitrogen flow. To this solution is added $Pd(dppf)CL_2$ (0.1 eq, 2.2 g) and the mixture is stirred at 55 °C for 1 hour. The mixture is diluted with DCM and filtered through a celite pad. Solids are thoroughly washed with DCM. The filtrate is washed with water and sat $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The residue is used without further purification.

3.83.2. Step ii : 2-Ethyl-4-bromo-6-fluoro-aniline

[0549] To a solution of 2-ethyl-6-fluoroaniline (1.0 eq, 3.7 g) in acetic acid (70 mL) is added bromine (1.1 eq, 1.5 mL) and the mixture is stirred at room temperature for 15 min. The mixture is neutralized by addition of an aqueous solution of NaOH and the product is extracted with DCM. The organic layer is successively washed with a solution of $Na_2S_2O_3$, water and brine, dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica chromatography (petroleum ether/EtOAc: 100/0 to 70/30) to afford the desired product.

3.83.3. Step iii : N-(4-Bromo-2-ethyl-6-fluoro-phenyl)-acetamide

[0550] To a solution of 2-ethyl-4-bromo-6-fluoroaniline (1.0 eq, 4.0 g), triethylamine (1.1 eq, 2.8 mL), DMAP, 0.1 eq, 200 mg) in DCM (50 mL) is added acyl chloride (1.1 eq, 1.5 mL) and the mixture is stirred at room temperature for 4 hours. The mixture is diluted with DCM and washed with water and a saturated solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue is triturated in petroleum ether and filtered to give the desired product.

3.83.4. Step iv : N-(2-Ethyl-6-fluoro-4-methylsulfanyl-phenyl)-acetamide

[0551] A mixture of N-(4-bromo-2-ethyl-6-fluoro-phenyl)-acetamide (1.0 eq, 1.0 g), methyl mercaptan (2.2 eq, 4.0 mL), DIPEA (2 eq, 1.35 mL) in dry dioxane (10 mL) is degassed under nitrogen flow. To this mixture is added Pd_2dba_3 (0.02 eq, 70 mg), Xantphos (0.08 eq, 165 mg) and the mixture is degassed again and stirred at 100 °C for 16 hours. The mixture is diluted with DCM and filtered through a celite pad. The filtrate is washed with water and a saturated solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue is used directly in the next step.

3.83.5. Step v: 2-Ethyl-6-fluoro-4-methylsulfanyl-aniline

[0552] A mixture of N-(2-ethyl-6-fluoro-4-methylsulfanyl-phenyl)acetamide (1.0 eq, crude) is diluted in THF (5 mL) and treated with a solution of HCl 2N (5 mL) and the resulting mixture is heated at 100°C for 16 hours. The mixture is diluted with DCM and f washed with water and a saturated solution of $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated. The residue is used directly in the next step.

3.83.6. Step vi: 2-Ethyl-6-fluoro-4-methylsulfonyl-aniline

[0553] To a solution of 2-ethyl-6-fluoro-4-methylsulfanyl-aniline (1.0 eq, crude) in THF (20 mL) and added mCPBA (3.0 eq, 2.0 g) and the resulting mixture is stirred at room temperature for 1 hour. The mixture is diluted with EtOAc and water. The two phases are separated and the aqueous layer is further extracted with EtOAc. The organic layers are combined and dried (Na_2SO_4), filtered and concentrated.

The residue is purified by silica chromatography (petroleum ether/EtOAc: 100/0 to 70/30) to afford the desired product.

3.83.7. Step vii: N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro 4-methanesulfonyl-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0554] A mixture of 2-Ethyl-6-fluoro-4-methylsulfonyl-aniline (0.92 mmol), N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine (0.92 mmol) and Cs_2CO_3 (2.30 mmol) in 1,4-dioxane (4 mL) is degased under a nitrogen flow. Pd(OAc)2 (0.18 mmol) and BINAP (0.28 mmol) are added and the resulting mixture is further degased and stirred at 100°C for 20 h. The reaction is stopped, diluted with DCM, filtered through a filter pad (SEITZ, K300 d60 mm). The filtrate is washed with sat $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated.. Purification by silica chromatography (DCM/ EtOAc: 100/0 to 0/100, followed by EtOAc/ NH_3 in MeOH: 100/0 to 95/5) to afford the desired product.

3.83.8. Step viii : N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro 4-methanesulfonyl-phenyl)- 1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0555] Methyl iodide (0.79 mmol) is added to a mixture of N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro 4-methanesulfonyl-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (0.26 mmol) and NaH (0.79 mmol) in THF at room temperature. The mixture is stirred for 1 h at room temperature. The mixture is diluted with EtOAc and quenched by addition of water. The organic layer is then washed with sat $NaHCO_3$, filtered through a phase separator and concentrated to afford the desired product.

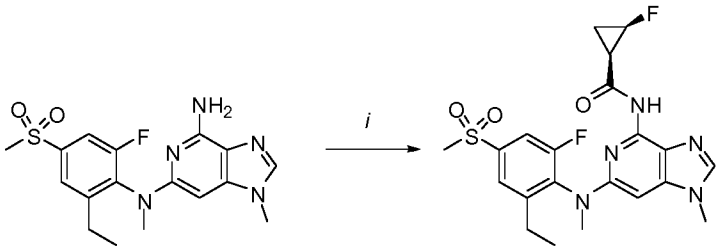
3.83.9. Step ix : N6-(2-ethyl-6-fluoro 4-methylsulfonyl-phenyl)- 1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0556] A mixture of of N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro 4-methanesulfonyl-phenyl)- 1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (0.26 mmol) in 1:1 THF/1N HCl is stirred at room temperature for 0.5 h. The mixture is diluted with water and EtOAc. The EtOAc layer is discarded. The aqueous layer is then basified with a solution of NaOH 1N and extracted with DCM. The organic layer is filtered through a phase separator and concentrated to afford the desired product.

3.83.10. Step x : N-(6-((2-ethyl-6-fluoro-4-(methylsulfonyl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

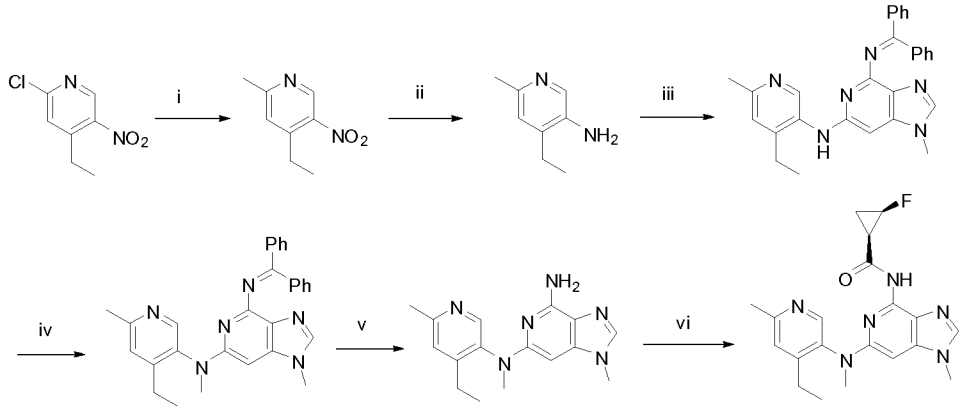
[0557] Synthesised following the same conditions used for Compound 82 (*step iv).*

3.84. Compound 84 (1R,2R)-N-(6-((2-ethyl-6-fluoro-4-(methylsulfonyl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



[0558] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (0.30 mmol) in dry DCM (1.5 mL) at 0 °C is added oxalyl chloride (0.30 mmol) followed by 2 drops of DMF. After 30 min, a suspension of N-(6-((2-ethyl-6-fluoro-4-(methylsulfonyl)phenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl) cyclopropanecarboxamide (0.15 mmol) in dry DCM (1.5 mL) is added portionwised, followed by pyridine (0.45 mmol), and the mixture is stirred for 2 h. LC-MS showed 50% conversion to the desired product. 1 mL of pyridine is added and the resulting mixture ws stirred for 2.5 h. The crude mixture is diluted with DCM and washed with NH_4Cl, filtered through a phase separator and concentrated. The residue is purified by preparatory HPLC.

3.85. Compound 85: (1R,2R)-N-(6-((4-ethyl-6-methylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide 85.



3.85.1. Step i : 4-ethyl-2-methyl-5-nitropyridine

[0559] 4-ethyl-2-chloro-5-nitro pyridine (1.0 eq, 200 mg), methyl boronic acid pinacol ester (2.5 eq, 150 mg), K_2CO_3 (3.0 eq, 450 mg) are dissolved in a mixture of dioxane and water (10/2.5 mL) and degassed under nitrogen flow. $Pd(dppf)CL_2$ (0.1 eq, 90 mg) is added and the mixture is stirred at 100 °C for 16 h. The mixture is diluted with EA and filtered through a celite pad. The filtrate is washed with a saturated solution of $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The crude is used without further purification.

3.85.2. Step ii : 4-ethyl-6-methyl-pyridin-3-ylamine

[0560] To a solution of 4-ethyl-2-methyl-5-nitro-pyridine (1.0 eq, 320 mg) in MeOH (7 mL) is added zinc powder (5.0 eq, 215 mg), NH_4Cl (cat.) and formic acid (1.5 mL). The resulting mixture is heated to room temperature for 30 min. The mixture is cooled to room temperature and filtered through celite pad and solids are washed with DCM. The filtrate is concentrated and the residue diluted in DCM, washed with a saturated solution of $NaHCO_3$, filtered through a hydrophobic frit and concentrated. The product is purified by silica chromatography (DCM/NH3 in MeOH: 100/0 to 95/5) to afford the desired product.

3.85.3. Step iii: N4-Benzhydrylidene-N6-(4-ethyl-6-methyl-pyridin-3-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0561] Synthesised following the same conditions used for Compound 62 (*step v*).

3.85.4. Step iv: N4-Benzhydrylidene-N6-(4-ethyl-6-methyl-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0562] Synthesised following the same conditions used for Compound 62 (*step vi).*

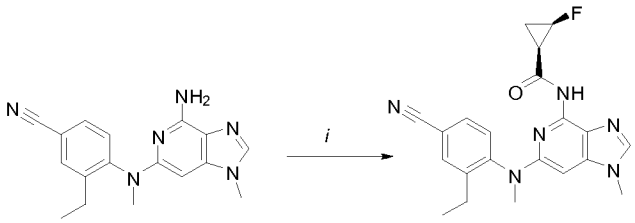
3.85.5. Step v: N6-(4-ethyl-6-methyl-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0563] Synthesised following the same conditions used for Compound 62 (*step vii).*

3.85.6. Step vi: (1R,2R)-N-(6-((4-ethyl-6-methylpyridin-3-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0564] Synthesised following the same conditions used for Compound 62 (*step viii).*

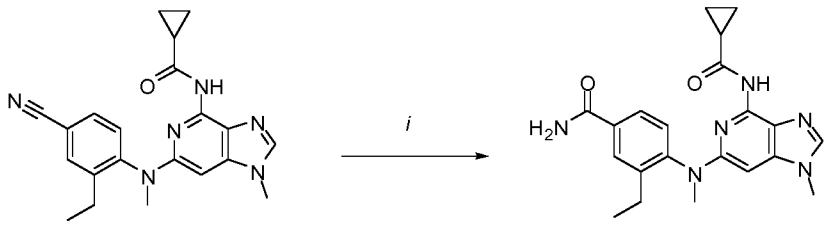
3.86. Compound 86: (1R,2R)-N-(6-((4-cyano-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.87. Step i : (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-ethylphenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0565] Synthesised following the same conditions used for Compound 64 (*step i).*

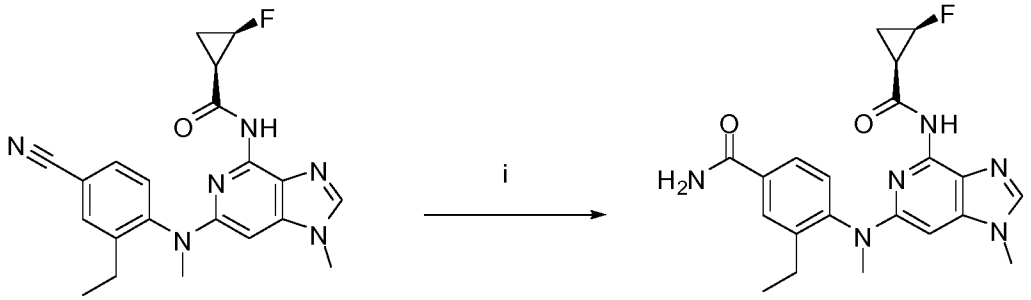
3.88. Compound 87: 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethylbenzamide



3.88.1. Step i : 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethylbenzamide

[0566] Synthesised following the same conditions used for Compound 68 (*step ii).*

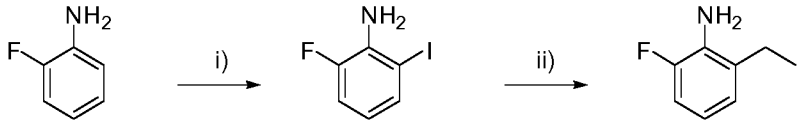
3.89. Compound 88: 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethylbenzamide



3.89.1. Step i : 4-((4-(cyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-3-ethylbenzamide

[0567] Synthesised following the same conditions used for Compound 68 (*step ii).*

3.90. Intermediate 18: 2-Ethyl-6-fluoroaniline



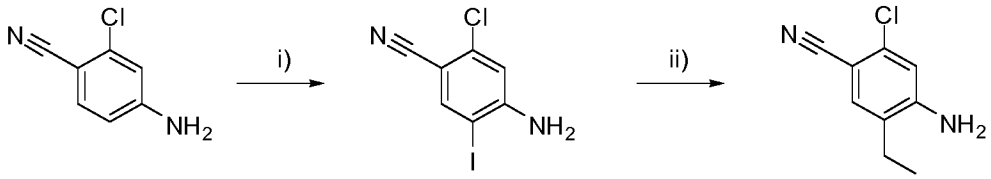
3.90.1. Step i): 6-Fluoro-2-iodoaniline

[0568] Iodine (1 eq, 4.6 g) is dissolved in EtOH (150 mL) at room temperature in a 250 mL round bottom flask and 2-fluoroaniline (1 eq, 2.0 g) and silver sulfate (1 eq, 5.6 g) are added. After overnight stirring of the suspension at room temperature, the silver salts are filtered off and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$ (3 x 50 mL). The organic layer is washed with sat. brine, dried over Na_2SO_4 and purified via silica chromatography (petroleum ether/EtOAc; 100:0 to 50:50) to give the envisaged product.

3.90.2. Step ii): 2-ethyl-6-fluoroaniline

[0569] $PdCl_2dppf$ (0.1 eq, 375 mg), Cs_2CO_3 (3 eq, 4.5 g) and 6-fluoro-2-iodoaniline (1 eq, 1.1 g) are dissolved in dry DMF (50 mL) in a 250 mL round bottom flask. The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of triethylborane (1M in hexane, 1.3 eq, 6.0 mL). The reaction is heated to 55°C for 2 h, using a condenser. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured into water and extraction with DCM (3 x 50 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 80:20) to give the desired product.

3.91. Intermediate 19: 4-amino-2-chloro-5-ethyl-benzonitrile



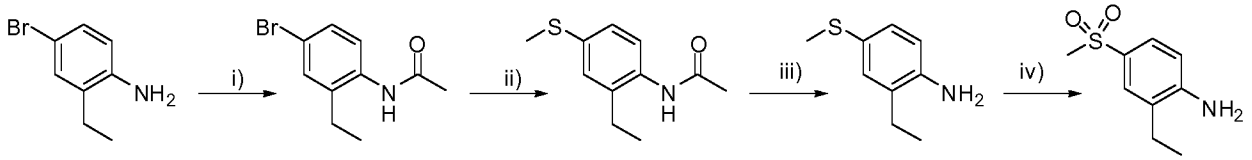
3.91.1. Step i): 4-amino-2-chloro-5-iodo-benzonitrile

[0570] Iodine (1 eq, 1.7 g) is dissolved in EtOH (75 mL) at room temperature in a 250 mL round bottom flask and 4-amino-2-chloro-benzonitrile (1 eq, 1.0 g) and silver sulfate (1 eq, 2.0 g) are added. After overnight stirring of the suspension at room temperature, the silver salts are filtered off and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$ (3 x 50 mL). The organic layer is washed with sat. brine, dried over Na_2SO_4 and concentrated to give a mixture of both regioisomers (87/13).

3.91.2. Step ii): 4-amino-2-chloro-5-ethyl-benzonitrile

[0571] $PdCl_2dppf$ (0.1 eq, 440 mg), Cs_2CO_3 (3 eq, 5.28 g) and 4-amino-2-chloro-5-iodo-benzonitrile (1 eq, 1.5 g) are dissolved in dry DMF (60 mL) in a 250 mL round bottom flask. The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of triethylborane (1M in hexane, 1.3 eq, 7.0 mL). The reaction is heated to 55°C for 2 h, using a condenser. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured into water and extraction with DCM (3 x 50 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 70:30) to give the desired product.

3.92. Intermediate 20: 2-Ethyl-4-methanesulfonyl-aniline



3.92.1. Step i): N-(2-ethyl-4-bromo-aniline)-acetamide

[0572] Acetyl chloride (1.1 eq, 785 µL) is added to a solution of 2-ethyl-4-bromoaniline (1.0 eq, 2.0 g), triethylamine (1.1 eq, 1.5 mL) and DMAP (0.1 eq, 120 mg) in anhydrous DCM (25 mL) at room temperature in a 100 mL round bottom flask. After 30 min stirring at room temperature, the reaction mixture is diluted with DCM and washed with water and sat. $NaHCO_3$. The organic layer is washed with sat. $NaHCO_3$, dried over Na_2SO_4. The residue is triturated in petroleum ether and filtered to give the envisaged product.

3.92.2. Step ii): N-(2-ethyl-4-methanesulfanyl-aniline)-acetamide

[0573] N-(2-ethyl-4-bromo-aniline)-acetamide (1.0 eq, 1.0 g), sodium thiomethoxide (1.0 eq, 1.2 mL), DIPEA (2.0 eq, 1.4 mL) are dissolved in dioxane (10 mL) in a 20 mL MW tube. The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of Pd_2dba_3 (0.02 eq, 75 mg) and Xantphos (0.08 eq, 160 mg). The reaction is heated to 100°C for 1 h in a sealed tube. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad, which is washed with EA. The filtrate is washed with sat. $NaHCO_3$. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*.

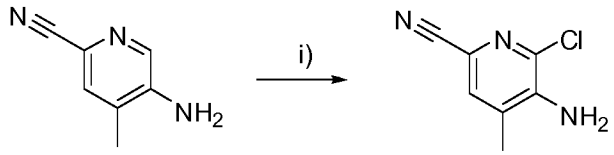
3.92.3. Step iii): 2-ethyl-4-methanesulfanyl-aniline

[0574] N-(2-ethyl-4-methanesulfanyl-aniline)-acetamide (1.0 eq, 1.0 g) is treated with a solution of HCl in dioxane (4N, 5.0 mL). The reaction is heated to 100 °C. After overnight stirring at 100 °C, the mixture is diluted with EA and water. The aqueous layer is basified with a solution of NaOH (1.0 N, 10 mL) and the product is extracted with DCM. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*.

3.92.4. Step iv): 2-ethyl-4-methanesulfonyl-aniline

[0575] 2-ethyl-4-methanesulfanyl-aniline (1.0 eq, 330 mg) is dissolved in THF (5.0 mL) and mCPBA (2.0 eq, 250 mg) is added. The reaction is stirred at rt. Upon completion of the reaction, as shown by LC-MS, the mixture is diluted with DCM and water. The combined organic layers are washed with sat. $NaHCO_3$, dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 50:50) to give the desired product.

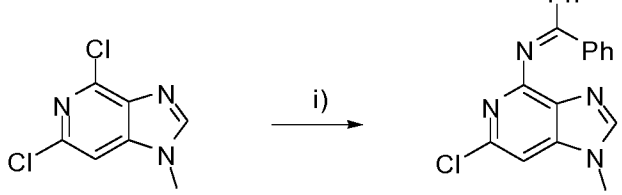
3.93. Intermediate 21: 5-amino-6chloro-4-methyl-pyridine-2-carbonitrile



3.93.1. Step i): 5-amino-6-chloro-4-methyl-pyridine-2-carbonitrile

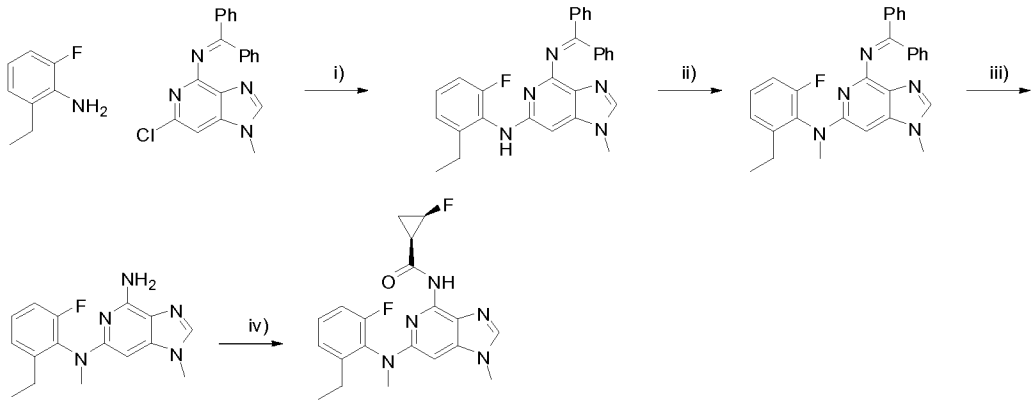
[0576] NCS (1 eq, 500 mg) and 5-amino-4-methyl-pyridine-2-carbonitrile (1.0 eq, 500 mg) wered isoolved in acetonitrile. The mixture is heated to 80 °C for 1h. upon completion of the reaction, as shwn by LC-MS, water is added and the precipitate is filtered to give the desired product.

3.94. Intermediate 22: Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridine-4-yl)amine



[0577] 4,6-dichloro-1-methyl-1H-imidazo[4,5-c]pyridin (1 eq, 2.0 g) and benzophenonimine (1.0 eq, 1.7 mL) and sodium tert-butoxide (1.5 eq, 1.4 g) are dissolved in toluene (40 mL). The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of $Pd(OAc)_2$ (0.1 eq, 225 mg) and BINAP (0.3 eq, 1.8 g). The mixture is heated to 80 °C for 4h. Upon completion of the reaction, as shown by LC-MS, the suspension is filtered over a Celite pad, which is washed with EA. The filtrate is washed with sat. $NaHCO_3$. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*. The residue is purified by silica chromatography (petroleum ether/EtOAc; 100:0 to 1:100, followed by EA/MeOH: 100:0 to 95:5) to give the desired product.

3.95. Compound 89: (1R,2R)-N-(6-((2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.95.1. Step i): N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0578] A degassed mixture of 2-ethyl-6-fluoroaniline (1.0 eq, 370 mg), Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridine-4-yl)amine (1.0 eq, 920 mg), $Pd(OAc)_2$ (0.2 eq, 120 mg), BINAP (0.3 eq, 500 mg) and Cs_2CO_3 (2.5 eq, 2.1 g) in dry dioxane (10 mL) in a sealed tube is heated at 100 °C for 16 h. The resulting mixture is diluted with EA and washed with sat. $NaHCO_3$. The combined organics is dried (Na_2SO_4) and concentrated. Purification by silica chromatography (petroleum ether/EtOAc; 100:0 to 0:100) affords the desired compound.

3.95.2. Step ii): N4-Benzhydrylidene-N6-(2-ethyl-6-fluoro-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0579] To the amine (1.0 eq, 780 mg) in dry THF (20 mL) is added NaH (2.0 eq, 140 mg). After 5 min, MeI (2.0 eq, 220 µL) is added and the mixture is stirred at room temperature for 2 h. The resulting mixture is diluted with EA and neutralised by addition of water. The combined organic layers are washed aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used directly in the next step without further purification.

3.95.3. Step iii): N6-(2-Ethyl-6-fluoro-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0580] To a solution of the crude benzophenonimine in THF (10 mL) is added aq. 2M HCl solution (10 mL) and the mixture is stirred at room temperature for 1.5 h. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The combined organic layers are dried (Na_2SO_4) and concentrated to afford the desired compound.

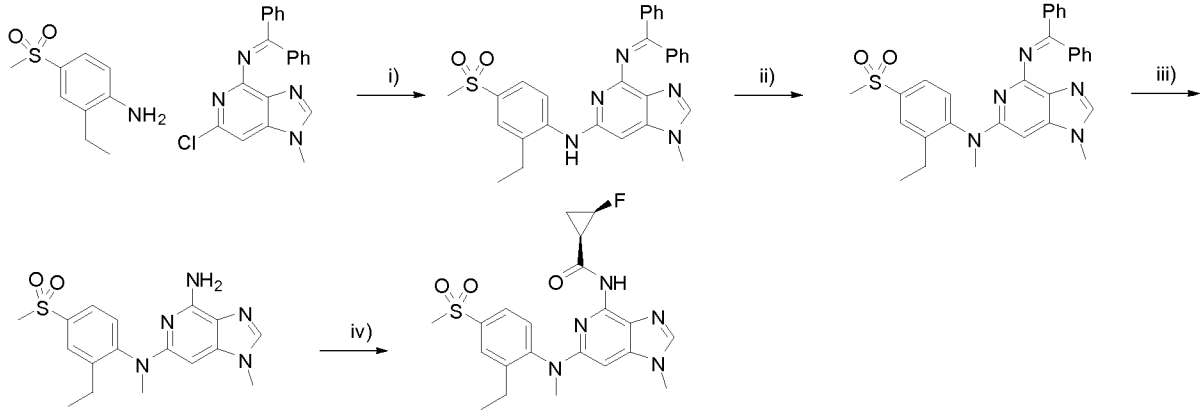
3.95.4. Step iv): (1R,2R)-N-(6-((2-ethyl-6-fluorophenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0581] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 80 mg) in dry DCM (1 mL) at 0 °C is added oxalyl chloride (1.5 eq, 65 µL) followed by 3-4 drops of DMF. After 5 min, a suspension of N6-(2-Ethyl-6-fluoro-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (1 eq, 150 mg) in dry DCM (2 mL) is added portionwised, followed by pyridine (120 µL), and the mixture is stirred for 16 h.

The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated. The residue is purified by preparative HPLC.

[0582] ^1H NMR δ (ppm) ($DMSO-d_6$): 9.82 (1 H, s br, NH), 7.97 (1 H, s, ArH), 7.31 (1 H, t, ArH), 7.15 (1 H, d, ArH), 7.09 (1 H, d, ArH), 6.30 (1 H, s, ArH), 4.70-4.50 (1H,d, CH), 3.66 (3 H, s, CH3), 3.33 (3 H, s, CH3), 2.67 (2H, q, CH2), 2.32 (1H, s, CH), 1.65-1.55 (1 H, d, CH), 1.21 (3 H, t, CH3), 1.01 (1H, s, CH).

3.96. Compound 90: (1R,2R)-N-(6-((2-ethyl-4-methanesulfonyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide (



3.96.1. Step i: N4-Benzhydrylidene-N6-(2-ethyl-4-methanesulfonyl-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0583] Prepared following step i*)* of compound 89 starting from 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.1 eq, 475 mg) and 2-ethyl-4-methanesulfonyl-aniline (1.0 eq, 250 mg).

3.96.2. Step ii: N4-Benzhydrylidene-N6-(2-ethyl-4-methanesulfonyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0584] Prepared following step *ii)* of compound 89 starting from a crude of N4-Benzhydrylidene-N6-(2-ethyl-4-methanesulfonyl-phenyl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

3.96.3. Step iii: N6-(2-Ethyl-4-methanesulfonyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0585] Prepared following step *iii)* of compound 89 starting from N4-Benzhydrylidene-N6-(2-ethyl-4-methanesulfonyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine.

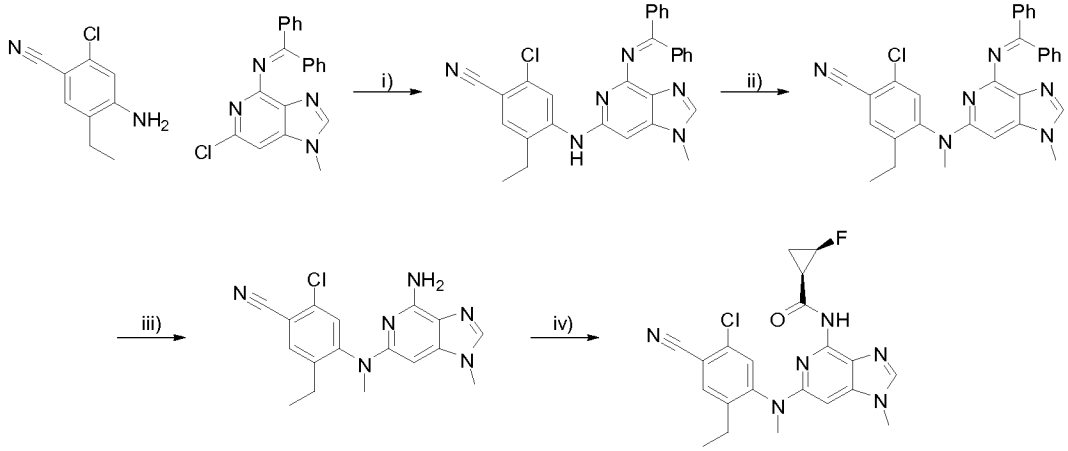
3.96.4. Step iv: (1R,2R)-N-(6-((2-ethyl-4-methanesulfonyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0586] Prepared following step *iv)* of compound 89 starting from (R,R)-2-fluoro-cyclopropanecarboxylic acid (2.0 eq, 50 mg) and N6-(2-Ethyl-4-methanesulfonyl-phenyl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine (1.0 eq, 100 mg). The residue is purified by preparative HPLC.

[0587] ^1H NMR δ (ppm) ($DMSO-d_6$): 9.83 (1 H, s br, NH), 7.99 (1 H, s, ArH), 7.88 (1 H, d, ArH), 7.82 (1 H, dd, ArH), 7.45 (1 H, d, ArH), 6.29 (1 H, s, ArH), 4.75-4.45 (1H, d, CH), 3.68 (3 H, s, CH3), 3.35 (3

H, s, CH3), 3.27 (3 H, s, CH3), 2.55 (2H, q, CH2), 2.36 (1H, s, CH), 1.63-1.56 (1 H, d, CH), 1.12 (3 H, t, CH3),0.98 (1H, s, CH).

3.97. Compound 91: (1R,2R)-N-(6-((2-chloro-5-ethyl-benzonitrile)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.97.1. Step i: 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-2-chloro-5-ethyl-benzonitrile

[0588] Prepared following step i*)* of compound 89 starting from 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.0 eq, 1.5 g) and 4-amino-2-chloro-5-ethyl-benzonitrile.

3.97.2. Step ii: 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-2-chloro-5-ethyl-benzonitrile

[0589] Prepared following step *ii)* of compound 89 starting from a crude of 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-2-chloro-5-ethyl-benzonitrile.

3.97.3. Step iii: 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-2-chloro-5-ethyl-benzonitrile

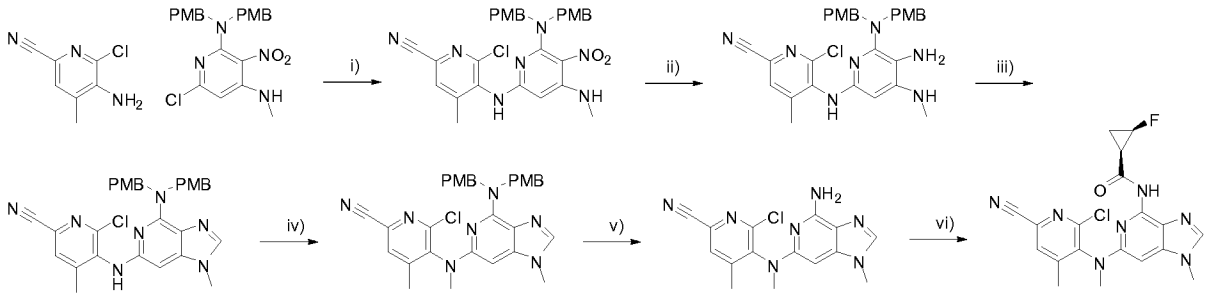
[0590] Prepared following step *iii)* of compound 89 starting from 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-2-chloro-5-ethyl-benzonitrile as crude.

3.97.4. Step iv: (1R,2R)-N-(6-((2-chloro-5-ethyl-benzonitrile)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0591] Prepared following step *iv)* of compound 89 starting from (R,R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 70 mg) and 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-2-chloro-5-ethyl-benzonitrile (1.0 eq, 150 mg). the residue is purified by preparative HPLC.

[0592] ^{1}H NMR δ (ppm) ($CDCl_3$): 8.23 (1 H, s br, NH), 7.67 (1 H, s, ArH), 7.36 (1 H, s, ArH), 5.81 (1 H, s, ArH), 4.71-4.55 (1H, d, CH), 3.77 (3 H, s, CH3), 3.44 (3 H, s, CH3), 2.74 (1H, s, CH), 2.49 (2H, q, CH2), 2.02-1.95 (2 H, m, CH2), 1.16 (3 H, t, CH3), 1.09 (1H, s, CH).

3.98. Compound 92: (1R,2R)-N-(6-(6-chloro-4-ethyl-pyridine-2-carbonitrile)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



3.98.1. Step i: 5-{6-[Bis-(4-methoxy-benzyl)-amino]-4-methylamino-5-nitro-pyridin-2-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile

[0593] A mixture of 6-chloro-N2,N2-bis(4-methoxybenzyl)-N4-methyl-3-nitropyridine-2,4-diamine (1.0 eq, 1.2 g), 5-amino-6-chloro-4-methyl-pyridine-2-carbonitrile (1.0 eq, 450 mg) and Cs_2CO_3 (2.5 eq, 1.5 g) in DMF (10 mL) is stirred at 100 °C for 16 h. Upon completion of the reaction, as shown by LC-MS, the mixture is partiotionned between DCM and water. The organic layer is washed with sat. $NaHCO_3$. The combined organic layers are dried (Na_2SO_4), filtered and concentrated. The residue is purified by silica chromatography (petroleum ether/EA; 100:0 to 75/25) to give the desired product.

3.98.2. Step ii: 5-{5-Amino-6-[bis-(4-methoxy-benzyl)-amino]-4-methylamino-pyridin-2-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile

[0594] A mixture of 5-{6-[Bis-(4-methoxy-benzyl)-amino]-4-methylamino-5-nitro-pyridin-2-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile (1 eq, 560 mg), Zn (10 eq, 645 mg), and NH_4Cl (catalytic amount) in MeOH (10 mL) and THF (10 mL) in a 100 mL flask, is stirred at room temperature for 1.5 h. The suspension is filtered and the filtrate is concentrated. The residue is purified by silica chromatography (petroleum ether/EA; 100:0 to 40/60) to give the desired product.

3.98.3. Step iii: 5-{4-[Bis-(4-methoxy-benzyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile

[0595] 5-{5-Amino-6-[bis-(4-methoxy-benzyl)-amino]-4-methylamino-pyridin-2-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile (1 eq, 260 mg) and trimethylorthoformate (2.0 eq, 170 µL) are dissolved in acetonitrile (4 mL) and the resulting solution is heated to 80 °C. After 1 h stirring, the mixture is diluted with EA and washed with water, the organic layer is dried (Na_2SO_4), filtered and concentrated.

3.98.4. Step iv: 5-({4-[Bis-(4-methoxy-benzyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-6-chloro-4-ethyl-pyridine-2-carbonitrile

[0596] Prepared following step *ii)* of compound 89 starting from a crude of 5-{4-[Bis-(4-methoxy-benzyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino}-6-chloro-4-ethyl-pyridine-2-carbonitrile.

3.98.5. Step v: 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-chloro-4-ethyl-pyridine-2-carbonitrile

[0597] The solution of the crude 5-({4-[Bis-(4-methoxy-benzyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-6-chloro-4-ethyl-pyridine-2-carbonitrile and TFA (5 mL) is stirred at 50

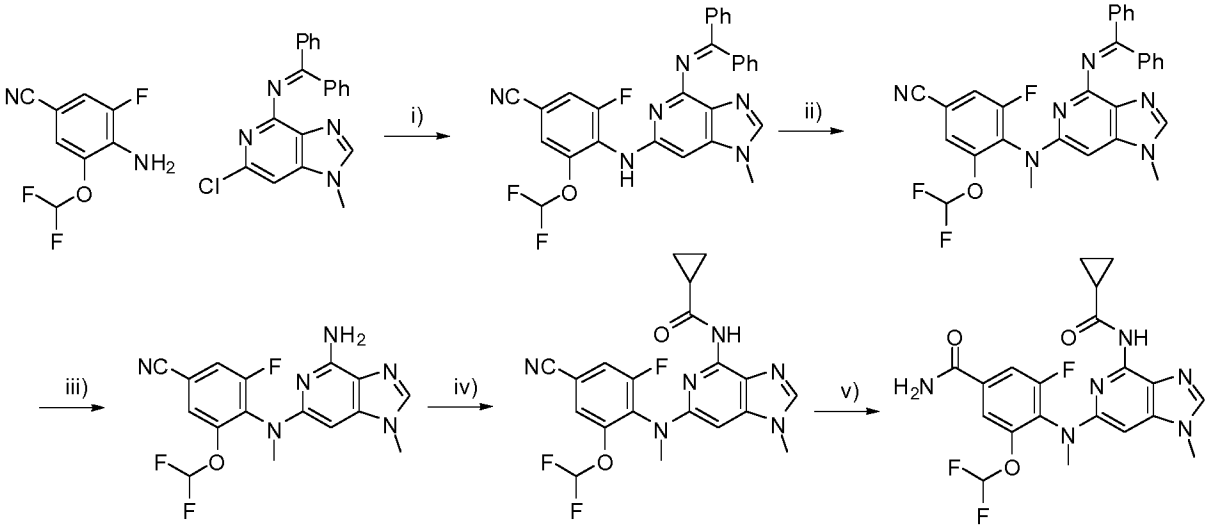
°C for 3 h. The mixture is neutralized by addition of sat. $NaHCO_3$ and the product is extracted with DCM. The combined organic layers are dried (Na_2SO_4), filtered and concentrated.

3.98.6. Step vi: (1R,2R)-N-(6-(6-chloro-4-ethyl-pyridine-2-carbonitrile)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide

[0598] A mixture of $(COCl)_2$ (2.0 eq, 85 µL), (R,R)-2-fluoro-cyclopropanecarboxylic acid (2.0 eq, 105 mg) and DMF (2 drops) in DCM (2 mL) is stirred at 0 °C for 30 min. A solution of 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-chloro-4-ethyl-pyridine-2-carbonitrile (1.0 eq, 150 mg) in DCM (3 mL) and pyridine (2.0 eq, 120 µL) are added in this order. The mixture is left to stir at room temperature for 1 h. The mixture is diluted with DCM, washed with sat. NH_4Cl, dried (Na_2SO_4) and concentrated. The mixture is purified by silica chromatography (petroleum ether/EA: 100:0 to 0:100, followed by EA/MeOH 100:0 to 96:4) and subsequently by preparative HPLC to yield the desired product.

[0599] ^{1}H NMR δ (ppm) (DMSO-d_6): 9.96 (1 H, s br, NH), 8.17 (1 H, s, ArH), 8.01 (1 H, s, ArH), 6.48 (s br, 1H, ArH), 4.80-4.60 (1 H, d, CH), 3.73 (3 H, s, CH3), 3.28 (3 H, s, CH3), 2.24 (m, 1H, CH), 2.21 (3 H, s, CH3), 1.61-1.53 (1 H, d, CH), 1.01 (1H, s, CH).

3.99. Compound 93: 4-{[4-(Cyclopropanecarbonyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-difluoromethoxy-5-fluoro-benzamide



3.99.1. Step i): 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-difluoromethoxy-5-fluoro-benzonitrile

[0600] A degassed mixture of the amine (1.0 eq, 184 mg), the chloroaryl (1.2 eq, 378 mg), $Pd(OAc)_2$ (0.2 eq, 40 mg), BINAP (0.3 eq, 168 mg) and Cs_2CO_3 (4.5 eq, 1.34 g) in dry dioxane (5 mL) in a sealed tube is heated at 110 °C for 3 h. The resulting mixture is diluted with EtOAc, washed with aq. sat. $NaHCO_3$, dried and concentrated. Purification by silica chromatography (EtOAc/petrol ether; 20:80 to 100:0 then EtOAc/PE; 1:1 to 1:0) affords the desired compound.

3.99.2. Step ii): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-difluoromethoxy-5-fluoro-benzonitrile

[0601] To the amine (1.0 eq, 350 mg) in dry THF (5 mL) is added NaH (3.0 eq, 82 mg). After 5 min, MeI (3.0 eq, 126 µL) is added and the mixture is stirred at room temperature until completion. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used directly in the next step without further purification.

3.99.3. Step iii): 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-difluoromethoxy-5-fluoro-benzonitrile

[0602] To a solution of the crude benzophenonimine in THF (3 mL) is added aq. 2M HCl solution (3 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated to afford the desired compound.

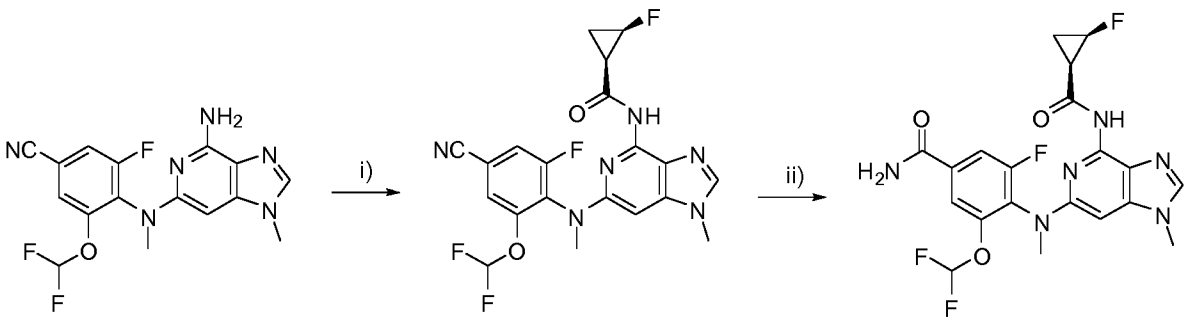
3.99.4. Step iv): Cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0603] To a solution of the amine (1.0 eq, 100 mg) and pyridine (0.25 mL) in DCM (2.5 mL) is added cyclopropane carbonyl chloride (1.2 eq, 31 µL) and the resulting mixture is stirred at room temperature for 1 h. The mixture is diluted with DCM and washed with aq. sat. $NaHCO_3$, filtered through a phase separator and concentrated.

3.99.5. Step v): 4-{[4-(Cyclopropanecarbonyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-difluoromethoxy-5-fluoro-benzamide

[0604] A mixture of the crude nitrile, aq. 1N NaOH (250µL) and H_2O_2 (35% in water, 200 µL) in EtOH (2 mL) and DMSO (0.5 mL) is heated at 50°C for 3 h. The mixture is diluted with DCM and washed with aq. sat. $NaHCO_3$, filtered through a phase separator and concentrated. Purification preparative HPLC affords the desired compound.

3.100. Compound 94: 3-Difluoromethoxy-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-benzamide



3.100.1. Step i): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

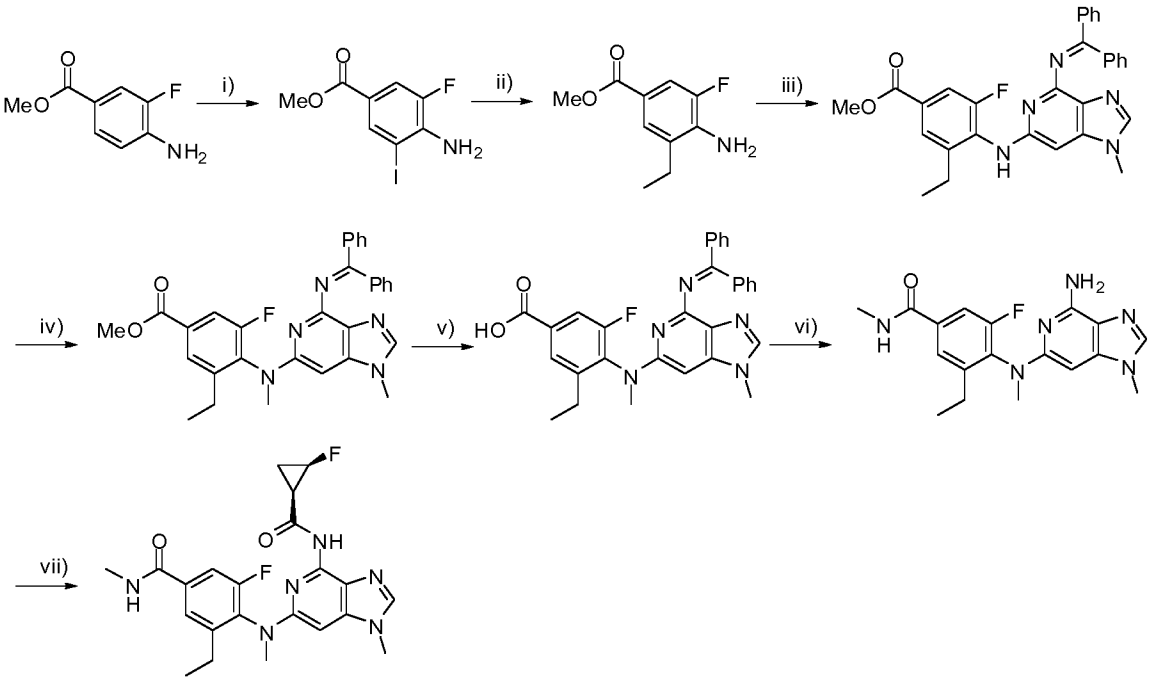
[0605] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (1.5 eq, 44 mg) in dry DCM (2.5 mL) at 0 °C is added oxalyl chloride (1.5 eq, 36 µL) followed by 1 drops of DMF. After 5 min, a suspension of the

amine (1 eq, 100 mg) in dry DCM (2 mL) is added portionwised, followed by pyridine (0.25 mL), and the mixture is stirred for 2 h. The mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated to give a crude mixture that is used directly in the next step without further purification.

3.100.2. Step ii): 3-Difluoromethoxy-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-benzamide

[0606] Prepared following step iv) of compound 89 starting from (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-cyano-2-difluoromethoxy-6-fluoro-phenyl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide.

3.101. Compound 95: 4-{[4-(Cyclopropanecarbonyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-difluoromethoxy-5-fluoro-benzamide



3.101.1. Step i): 4-Amino-3-fluoro-5-iodo-benzoic acid methyl ester

[0607] Iodine (1 eq, 3.76 g) is dissolved in EtOH (80 mL) at room temperature followed by the addition of 4-amino-3-fluoro-benzoic acid methyl ester (1 eq, 2.5 g) and silver sulfate (1 eq, 4.61 g). After 1h, the silver salts are filtered off and the filtrate is concentrated under reduced pressure. The residue is dissolved in DCM and washed with sat. $Na_2S_2O_3$, passed through a phase separator and concentrated to afford the desired product that is used as such in the next step.

3.101.2. Step ii): 4-Amino-3-ethyl-5-fluoro-benzoic acid methyl ester

[0608] $PdCl_2dppf$ (0.1 eq, 1.21 g), Cs_2CO_3 (3 eq, 14.5 g) and 4-fluoro-2-iodoaniline are dissolved in dry DMF (80 mL). The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of triethylborane (1M in hexane, 1.3 eq, 19 mL). The reaction is heated to 60°C for 18 h. The suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by silica chromatography (petroleum ether/EtOAc; 80:20) to give the desired product.

3.101.3. Step iii): 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzoic acid methyl ester

[0609] Prepared following step *i)* of compound 93 starting from 4-Amino-3-ethyl-5-fluoro-benzoic acid methyl ester and benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine.

3.101.4. Step iv): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzoic acid methyl ester

[0610] Prepared following step *ii)* of compound 93 starting from 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-5-fluoro-benzoic acid methyl ester.

3.101.5. Step v): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzoic acid

[0611] A mixture of the methyl ester (1 eq 0.75 g), sodium hydroxide (1.05 eq, 60 mg) in THF (12 mL) and water (2 mL) is heated at 100°C for 20 min in microwave reactor. The mixture is concentrated and used as such in the next step.

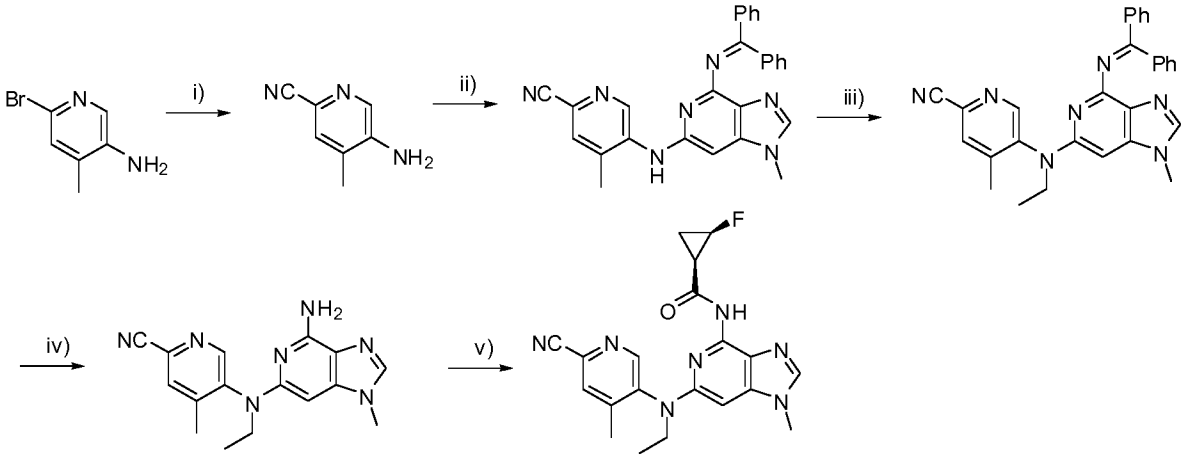
3.101.6. Step vi): 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-N-methyl-benzamide

[0612] To the carboxylic acid (1 eq, 200 mg) and triethylamine (3 eq, 163 µL) in DMF (2 mL), is added HATU (1.1 eq, 163 mg) and methylamine (2M in THF, 5 eq, 0.98 mL). The resulting mixture is stirred overnight at room temperature after what aq. 2M HCl (1 mL) is added and the mixture for 30 min. The reaction is diluted with EtOAc and extracted with aq. 2M HCl. The aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The combined organics is dried and concentrated to afford the desired compound.

3.101.7. Step vii): 4-{[4-(Cyclopropanecarbonyl-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-difluoromethoxy-5-fluoro-benzamide

[0613] Prepared following step iv*)* of compound 89 starting from 4-[(4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-5-fluoro-N-methyl-benzamide. Purification preparative HPLC affords the desired compound.

3.102. Compound 96: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-4-methyl-pyridin-3-yl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.102.1. Step i): 5-Amino-4-methyl-pyridine-2-carbonitrile

[0614] $Pd(PPh_3)_4$ (0.1 eq, 381 mg), zinc cyanide (1.6 eq, 626 mg) and 6-bromo-4-methyl-pyridin-3-ylamine (1 eq, 622 mg) are dissolved in anhydrous DMF (15 mL) in a microwave tube. The reaction mixture is heated to 150°C for 5 min under microwave irradiation. The reaction mixture is cooled down and poured into aq. sat. $NaHCO_3$. Extraction with EtOAc (3x) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuo*.The crude residue is triturated with Et_2O to afford the desired compound.

3.102.2. Step ii): 5-(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-4-methyl-pyridine-2-carbonitrile

[0615] Prepared following step *i)* of compound 93 starting from 5-amino-4-methyl-pyridine-2-carbonitrile and benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine.

3.102.3. Step iii): 5-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-ethyl-amino}-4-methyl-pyridine-2-carbonitrile

[0616] To the amine (1.0 eq, 230 mg) in dry DMF (3 mL) is added NaH (60% dispersion, 2.0 eq, 42 mg). After 5 min, ethyl iodide (2.0 eq, 85 µL) is added and the mixture is stirred at room temperature for 1 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give a crude mixture that is used directly in the next step without further purification.

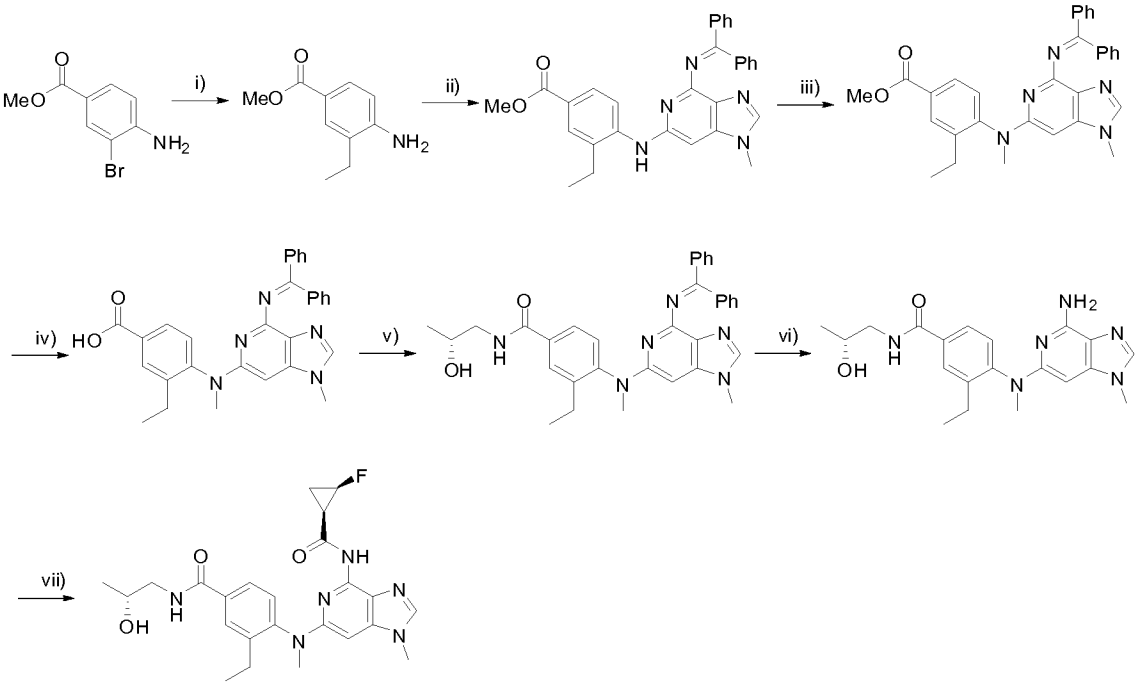
3.102.4. Step iv): 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-ethyl-amino]-4-methyl-pyridine-2-carbonitrile

[0617] Prepared following step *iii)* of compound 93 starting from 5-{[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-ethyl-amino}-4-methyl-pyridine-2-carbonitrile.

3.102.5. Step v): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-4-methyl-pyridin-3-yl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0618] Prepared following step iv*)* of compound 89 starting from 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-ethyl-amino]-4-methyl-pyridine-2-carbonitrile. Purification preparative HPLC affords the desired compound.

3.103. Compound 97: 3-Ethyl-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-N-((R)-2-hydroxy-propyl)-benzamide



3.103.1. Step i): 4-Amino-3-ethyl-benzoic acid methyl ester

[0619] $PdCl_2dppf$ (0.1 eq, 939 mg), Cs_2CO_3 (4 eq, 15 g) and 4-amino-3-bromo-benzoic acid methyl ester (1 eq, 2.65 g) are dissolved in dry DMF (30 mL). The suspension is degassed under nitrogen atmosphere for 10 min, followed by the addition of triethylborane (1M in hexane, 1.3 eq, 15 mL). The reaction is heated to 60°C for 1 h. The suspension is filtered over a Celite pad, which is washed with DCM. The filtrate is poured aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by silica chromatography (petroleum ether/EtOAc; 90:30) to give the desired product.

3.103.2. Step ii): 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-benzoic acid methyl ester

[0620] Prepared following step *i)* of compound 93 starting from 4-amino-3-ethyl-benzoic acid methyl ester and benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine.

3.103.3. Step iii): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-benzoic acid methyl ester

[0621] Prepared following step *ii)* of compound 93 starting from 4-[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-3-ethyl-benzoic acid methyl ester.

3.103.4. Step iv): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-benzoic acid

[0622] A mixture of the methyl ester (1 eq 0.75 g), sodium hydroxide (1 eq, 81 mg) in THF (12 mL) and water (2 mL) is heated at 100°C for 120 min in microwave reactor. The mixture is concentrated, triturated with Et_2O to afford the desired compound.

3.103.5. Step v): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide

[0623] A mixture of the carboxylic acid (1 eq, 120 mg), HOBt (1 eq, 34 mg), EDC (1.2 eq, 58 µL) and (R)-1-amino-propan-2-ol (2 eq, 39 µL) in DCM (5 mL) is stirred at room tempeture for 2 h. The resulting mixture is diluted with DCM and aq. sat. $NaHCO_3$, passed through a phase separator and concentrated.

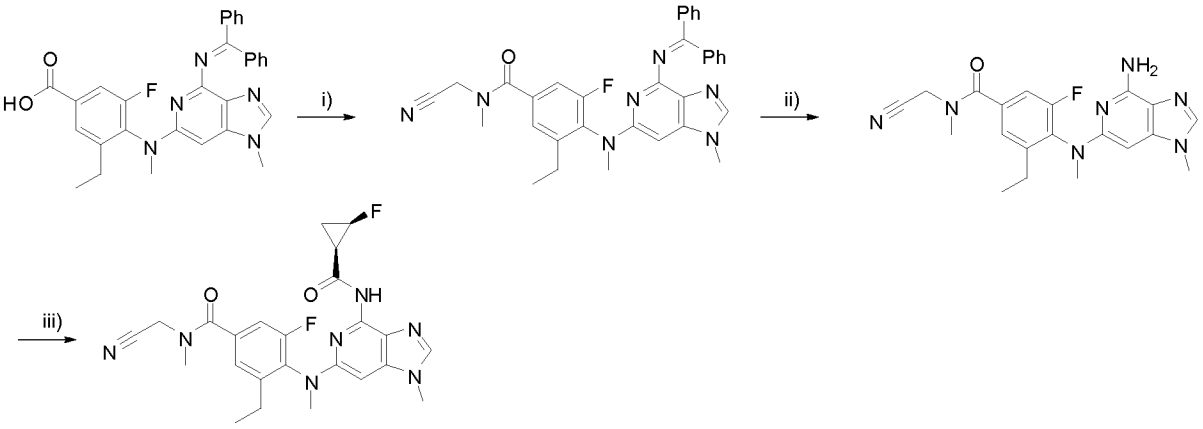
3.103.6. Step vi): 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide

[0624] Prepared following step *iii)* of compound 93 starting from 4-{[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide.

3.103.7. Step vii): 3-Ethyl-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-N-((R)-2-hydroxy-propyl)-benzamide

[0625] Prepared following step iv*)* of compound 89 starting from 4-[(4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide. Purification preparative HPLC affords the desired compound.

3.104. Compound 98: N-Cyanomethyl-3-ethyl-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-N-methyl-benzamide



3.104.1. Step i): 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-N-cyanomethyl-3-ethyl-5-fluoro-N-methyl-benzamide

[0626] To the carboxylic acid (1 eq, 200 mg) and triethylamine (12 eq, 0.65 mL) in DMF (2 mL), is added HATU (1.5 eq, 222 mg) and methylamino-acetonitrile hydrochloride (4 eq, 166 mg). The resulting mixture is stirred overnight at room The reaction is diluted with DCM and water, passed through a phase separator and concentrated to afford the desired compound.

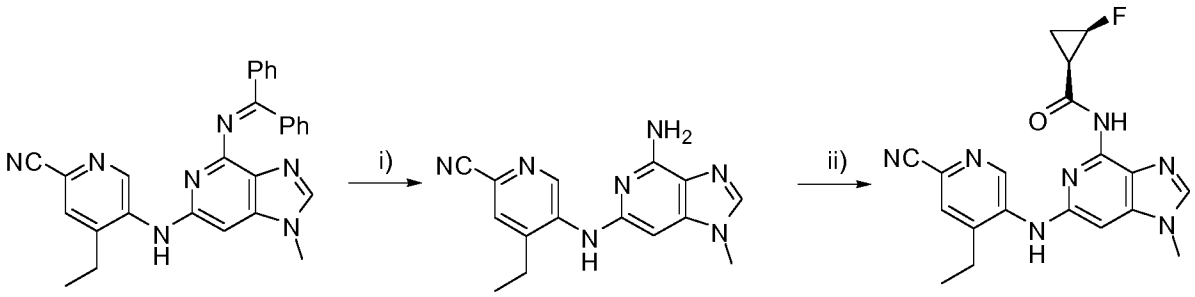
3.104.2. Step ii): 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-N-cyanomethyl-3-ethyl-5-fluoro-N-methyl-benzamide

[0627] Prepared following step *iii)* of compound 93 starting from 4-{[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide.

3.104.3. Step iii): N-Cyanomethyl-3-ethyl-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-N-methyl-benzamide

[0628] Prepared following step iv*)* of compound 89 starting from 4-[(4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide. Purification preparative HPLC affords the desired compound.

3.105. Compound 99: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(6-cyano-4-ethyl-pyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-amide



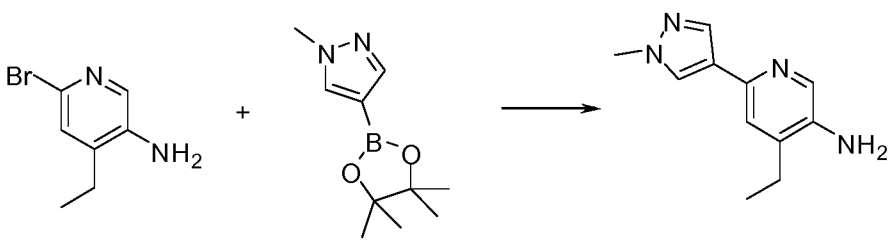
3.105.1. Step i): 5-(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-4-ethyl-pyridine-2-carbonitrile

[0629] Prepared following step *iii)* of compound 93 starting from 4-{[4-(benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-N-((R)-2-hydroxy-propyl)-benzamide.

3.105.2. Step ii): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid [6-(6-cyano-4-ethyl-pyridin-3-ylamino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl]-amide

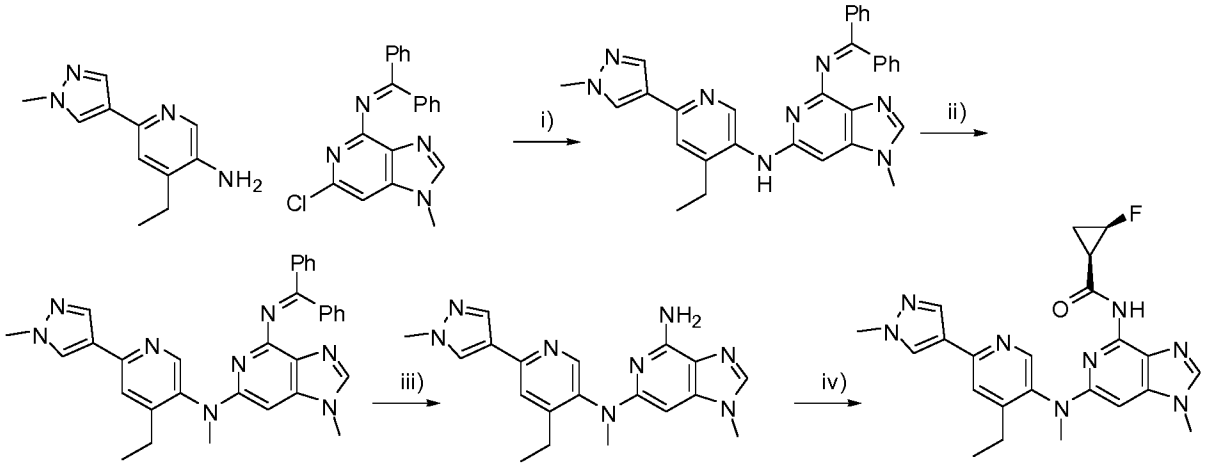
[0630] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (4 eq, 83 mg) in dry DCM (2 mL) at 0 °C is added oxalyl chloride (2.0 eq, 34 µL) followed by 1 drops of DMF. After 5 min, a suspension of the amine (1 eq, 60 mg) in dry DCM (1 mL) is added portionwised, followed by pyridine (64 µL), and the mixture is stirred for 2 h. The mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, dried and concentrated. Purification preparative HPLC affords the desired compound.

3.106. Intermediate 23: 4-Ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-ylamine



[0631] 6-bromo-4-ethylpyridin-3-ylamine (1.0 eq, 100 mg), the pyrazole boronic ester (1.3 eq, 135 mg) and Et_3N (3 eq, 0.21 mL) are dissolved 1,4-dioxane (3 mL) and water (1mL) in a microwave tube and the suspension is degassed under nitrogen atmosphere for 10 min. $PdCl_2dppf$ (0.05 eq, 20.3 mg) is added. The reaction mixture is brought to 85°C and is kept at this temperature for 4h. After completion of the reaction as shown by LC-MS, the mixture is diluted with water and EtOAc. Extraction with EtOAc (3 x 50 mL) is performed. The combined organics are washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure affords the desired product.

3.107. Compound 100: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[4-ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide



3.107.1. Step i): N-4-Benzhydrylidene-N-6-[4-ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0632] A degassed mixture of the amine (1.1 eq, 100 mg), the chloroaryl (1.0 eq, 157 g), $Pd(OAc)_2$ (0.2 eq, 20 mg), BINAP (0.3 eq, 85 mg) and Cs_2CO_3 (2.5 eq, 368 mg) in dry dioxane (2 mL) in a sealed tube is heated at 110 °C for 2 h. The resulting mixture is diluted in EtOAc and water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, the crude is used as such in the following step.

3.107.2. Step ii): N-4-Benzhydrylidene-N-6-[4-ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-1,N-6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0633] To the crude amine (1.0 eq, 0.494 mmol) in dry THF (5 mL) is added NaH (3.0 eq, 36 mg). After 5 min, MeI (3.0 eq, 92 µL) is added and the mixture is stirred at room temperature for 1 h. The resulting mixture is diluted with EtOAc and aq. sat. $NaHCO_3$. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, and the crude is used as such in the following step.

3.107.3. Step iii): N-6-[4-Ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-1,N-6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

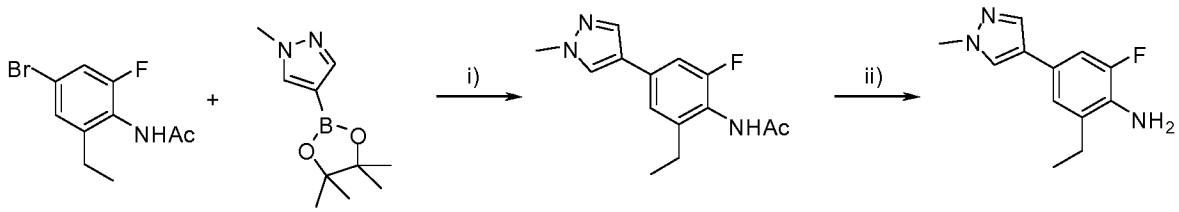
[0634] To a solution of the crude benzophenonimine in THF (1 mL) is added aq. 2M HCl solution (1 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with

EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is used as such in the following step.

3.107.4. Step iv): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[4-ethyl-6-(1-methyl-1H-pyrazol-4-yl)-pyridin-3-yl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0635] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 154 mg) in dry DCM (1 mL) at 0 °C is added oxalyl chloride (2.9 eq, 0.12 mL) followed by 1 drop of DMF. After 30 min, a suspension of the amine (1 eq, 178 mg) in dry DCM (1 mL) is added dropwise, followed by pyridine (4 eq, 0.16 mL), and the mixture is stirred at 0°C for 2 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.108. Intermediate 24: 2-Ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenylamine



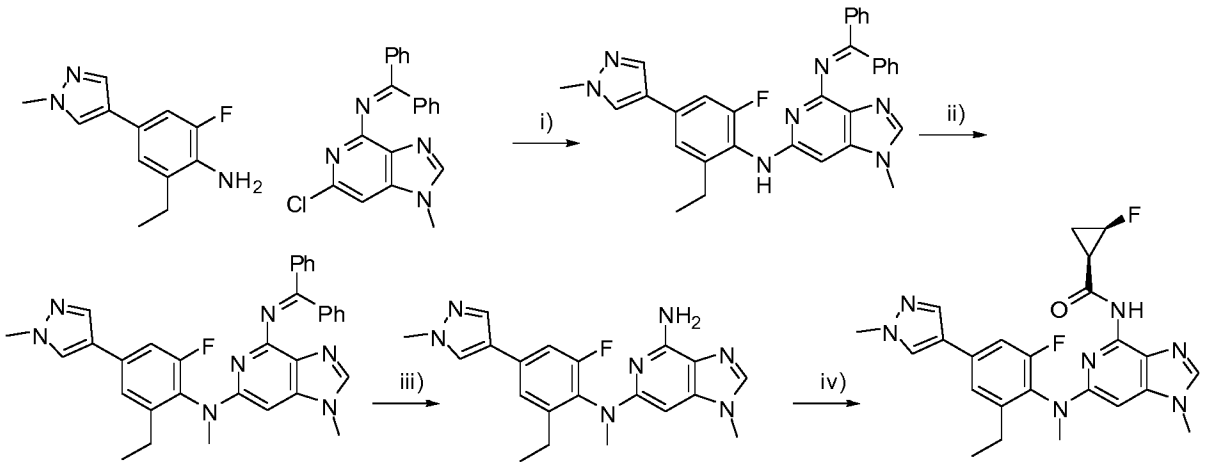
3.108.1. Step i): N-[2-Ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-acetamide

[0636] N-(4-Bromo-2-ethyl-6-fluoro-phenyl)-acetamide (1.0 eq, 400 mg), the pyrazole boronic ester (1.1 eq, 352 mg) and Et3N (3 eq, 0.64 mL) are dissolved 1,4-dioxane (8 mL) and water (2mL) in a microwave tube and the suspension is degassed under nitrogen atmosphere for 10 min. $PdCl_2dppf$ (0.05 eq, 63 mg) is added. The reaction mixture is brought to 85°C and is kept at this temperature for 3h. After completion of the reaction as shown by LC-MS, the mixture is diluted with water and EtOAc. Extraction with EtOAc (3 x 50 mL) is performed. The combined organics are washed with brine and dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the crude is used as such in the following step.

3.108.2. Step ii): 2-Ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenylamine

[0637] To a solution of the fluoroaryl in 1,4-dioxane (15 mL) is added aq. 6M HCl solution (10 mL) and the mixture is stirred at 100°C overnight. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is purified by silica chromatography (petroleum ether/EtOAc; 3:2) to give the desired product.

3.109. Compound 101: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[2-ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide



3.109.1. Step i): N-4-Benzhydrylidene-N-6-[2-ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0638] A degassed mixture of the amine (1.1 eq, 245 mg), the chloroaryl (1.0 eq, 353 g), $Pd(OAc)_2$ (0.2 eq, 46 mg), BINAP (0.3 eq, 191 mg) and Cs_2CO_3 (2.5 eq, 828 mg) in dry dioxane (4 mL) in a sealed tube is heated at 110 °C for 1h. The resulting mixture is diluted in EtOAc and water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, the crude is used as such in the following step.

3.109.2. Step ii): N-4-Benzhydrylidene-N-6-[2-ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1,N-6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0639] To the crude amine (1.0 eq, 1.12 mmol) in dry THF (11 mL) is added NaH (3.0 eq, 134 mg). After 5 min, MeI (3.0 eq, 210 µL) is added and the mixture is stirred at room temperature for 1 h. The resulting mixture is diluted with EtOAc and aq. sat. $NaHCO_3$. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, and the crude is used as such in the following step.

3.109.3. Step iii): N-6-[2-Ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1,N-6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

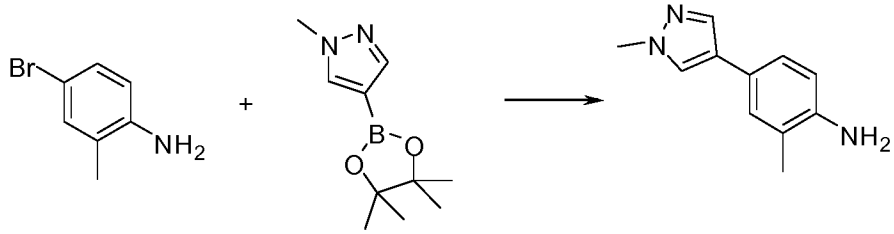
[0640] To a solution of the crude benzophenonimine in THF (2 mL) is added aq. 2M HCl solution (2 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is used as such in the following step.

3.109.4. Step iv): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[2-ethyl-6-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0641] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 350 mg) in dry DCM (3 mL) at 0 °C is added oxalyl chloride (2.9 eq, 0.28 mL) followed by 1 drop of DMF. After 30 min, a suspension of the

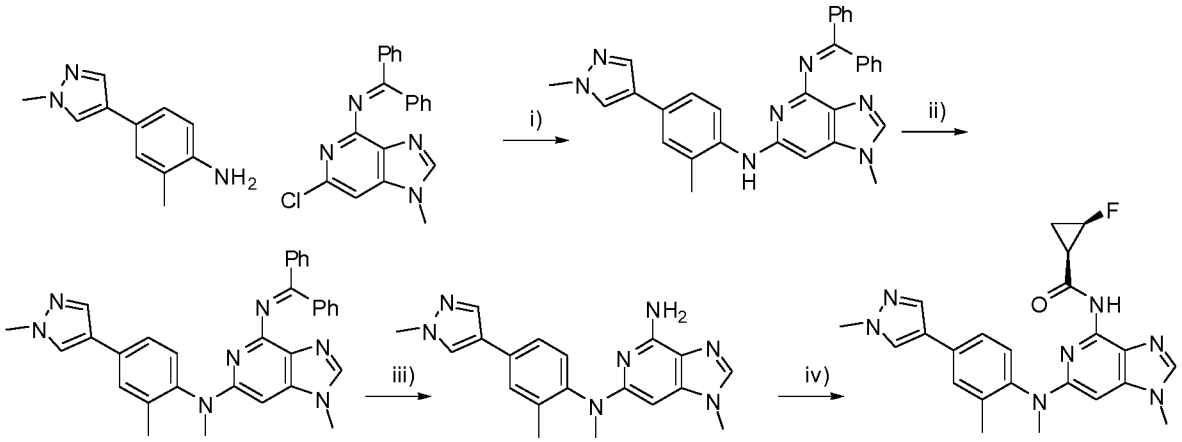
amine (1 eq, 1.12 mmol) in dry DCM (3 mL) is added dropwise, followed by pyridine (4 eq, 0.36 mL), and the mixture is stirred at 0°C for 6 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.110. Intermediate 25: 2-Methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenylamine



[0642] 4-Bromo-2-methyl-phenylamine (1.0 eq, 500 mg), the pyrazole boronic ester (1.3 eq, 616 mg) and K2CO3 (3 eq, 1.12 g) are dissolved 1,4-dioxane (12 mL) and water (3 mL) in a microwave tube and the suspension is degassed under nitrogen atmosphere for 10 min. $PdCl_2$dppf (0.05 eq, 110 mg) is added. The reaction mixture is brought to 85°C and is kept at this temperature for 4h. After completion of the reaction as shown by LC-MS, the mixture is diluted with water and EtOAc. Extraction with EtOAc (3 x 50 mL) is performed. The combined organics are washed with brine and dried over anhydrous Na_2SO_4. The mixture is concentrated to afford the desired product.

3.111. Compound 102: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (1-methyl-6-{methyl-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-amino}-1H-imidazo[4,5-c]pyridin-4-yl)-amide



3.111.1. Step i): N-4-Benzhydrylidene-1-methyl-N-6-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0643] A degassed mixture of the amine (1.1 eq, 298 mg), the chloroaryl (1.0 eq, 551 g), $Pd(OAc)_2$ (0.2 eq, 71 mg), BINAP (0.3 eq, 297 mg) and Cs_2CO_3 (2.5 eq, 1.30 g) in dry dioxane (6 mL) in a sealed tube is heated at 110 °C for 2h. The resulting mixture is diluted in EtOAc and water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, the crude is used as such in the following step.

3.112. Step ii): N-4-Benzhydrylidene-1,N-6-dimethyl-N-6-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0644] To the crude amine (1.0 eq, 1.59 mmol) in dry THF (16 mL) is added NaH (3.0 eq, 191 mg). After 5 min, MeI (3.0 eq, 0.30 mL) is added and the mixture is stirred at room temperature for 1 h. The resulting mixture is diluted with EtOAc and aq. sat. $NaHCO_3$. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, and the crude is used as such in the following step.

3.112.1. Step iii): 1,N-6-Dimethyl-N-6-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0645] To a solution of the crude benzophenonimine in THF (3 mL) is added aq. 2M HCl solution (3 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is used as such in the following step.

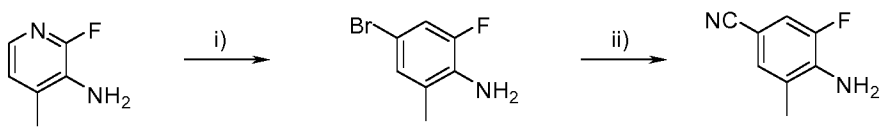
3.112.2. Step iv): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (1-methyl-6-{methyl-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-amino}-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0646] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 497 mg) in dry DCM (8 mL) at 0 °C is added oxalyl chloride (2.9 eq, 0.40 mL) followed by 1 drop of DMF. After 30 min, a suspension of the amine (1 eq, 1.59 mmol) in dry DCM (8 mL) is added dropwise, followed by pyridine (4 eq, 0.64 mL), and the mixture is stirred at 0°C for 6 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.112.3. Step iv): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (1-methyl-6-{methyl-[2-methyl-4-(1-methyl-1H-pyrazol-4-yl)-phenyl]-amino}-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0647] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 497 mg) in dry DCM (8 mL) at 0 °C is added oxalyl chloride (2.9 eq, 0.40 mL) followed by 1 drop of DMF. After 30 min, a suspension of the amine (1 eq, 1.59 mmol) in dry DCM (8 mL) is added dropwise, followed by pyridine (4 eq, 0.64 mL), and the mixture is stirred at 0°C for 6 h. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.113. Intermediate 26: 4-Amino-3-fluoro-5-methyl-benzonitrile



3.113.1. Step i): 4-Bromo-2-fluoro-6-methyl-phenylamine

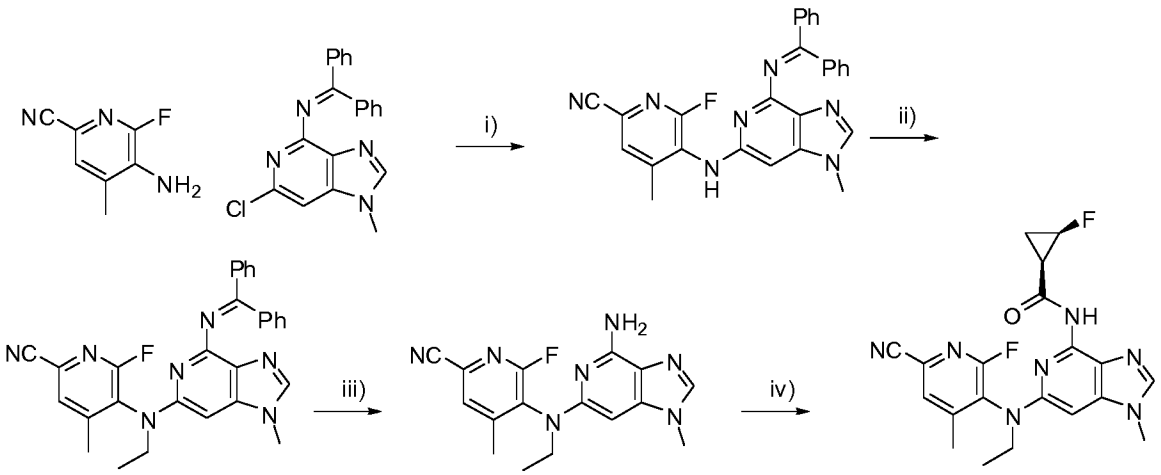
[0648] At room temperature, 2-Fluoro-6-methyl-phenylamine (1.0 eq, 5.0 g) and KOAc (1.0 eq, 3.9 g) are stirred in AcOH for 1h.At 0°C, BR^2 (1.0 eq, 2.04 mL) is added. The reaction mixture is kept at this temperature for 10 min. The resulting mixture is diluted with EtOAc. The organic phase is washed with

aq. sat. $NaHCO_3$ and aq. $Na_2S_2O_3$, dried over anhydrous Na_2SO_4. After concentration under reduced pressure, the residue is purified by silica chromatography (petroleum ether/EtOAc; 9:1 to 8:2) to give the desired product. (m = 7.6 g).

3.113.2. Step ii): 4-Amino-3-fluoro-5-methyl-benzonitrile

[0649] $Pd(PPh_3)_4$ (0.1 eq, 394 mg), zinc cyanide (1.6 eq, 642 mg) and 4-Bromo-2-fluoro-6-methyl-phenylamine (1 eq, 700 mg) are dissolved in anhydrous DMF (15 mL) in a 10 mL microwave tube. The suspension is brought to 150°C for 5 min under microwave irradiation (absorption level: high). The reaction mixture is cooled down and poured into water. Extraction with EtOAc (3 x 10 mL) is performed. The combined organic layers are dried (Na_2SO_4) and concentrated *in vacuum*. The crude residue is purified by silica chromatography (petroleum ether/EtOAc; 4:1, 2, or 3:2) to give the desired product.

3.114. Compound 103: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-2-fluoro-4-methyl-pyridin-3-yl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.114.1. Step i): 5-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0650] A degassed mixture of the amine (1.1 eq, 4.0 g), the chloroaryl (1.0 eq, 7.34 g), $Pd(OAc)_2$ (0.2 eq, 952 mg), BINAP (0.3 eq, 3.96 g) and Cs_2CO_3 (2.5 eq, 21.6 g) in dry dioxane (105 mL) in a sealed tube is heated at 110 °C for 2h. The resulting mixture is diluted in EtOAc and water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, the crude is purified by silica chromatography (petroleum ether/EtOAc; 9:1 to 4:1 to 0:1) to give the desired product.

3.114.2. Step ii): 5-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-ethyl-amino}-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0651] To the crude amine (1.0 eq, 0.390 mmol) in dry THF (3 mL) is added NaH (3.0 eq, 23.2 mg). After 5 min, EtI (3.0 eq, 47 µL) is added and the mixture is stirred at room temperature for 1 h. The resulting mixture is diluted with EtOAc and at 0°C is quenched with water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, and the crude is used as such in the following step.

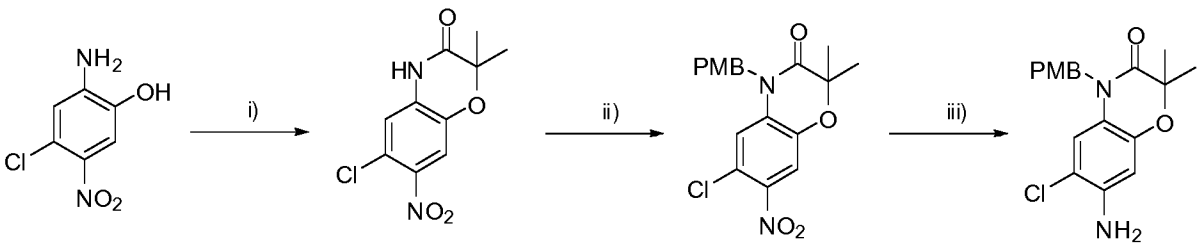
3.114.3. Step iii): 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-ethyl-amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0652] To a solution of the crude benzophenonimine in THF (1 mL) is added aq. 2M HCl solution (1 mL) and the mixture is stirred at room temperature for 30 min. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is used as such in the following step.

3.114.4. Step iv): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(6-cyano-2-fluoro-4-methyl-pyridin-3-yl)-ethyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0653] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 108 mg) in dry DCM (1 mL) at 0 °C is added oxalyl chloride (2.9 eq, 86 µL) followed by 1 drop of DMF. After 30 min, a suspension of the amine (1 eq, 0.345 mmol) in dry DCM (1.5 mL) is added dropwise, followed by pyridine (4 eq, 0.14 mL), and the mixture is stirred at 0°C for 2h, then warm up to room temperature overnight. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.115. Intermediate 27: 7-Amino-6-chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one



3.115.1. Step i): 6-Chloro-2,2-dimethyl-7-nitro-4H-benzo[1,4]oxazin-3-one

[0654] At room temperature, 2-Amino-4-chloro-5-nitro-phenol (1.0 eq, 5.0 g) is added to 2-bromo-2methylpropionic acid ethyl ester (2.0 eq, 7.8 mL) and KF (2.5 eq, 3.85 g) in DMF (110 mL). The suspension is brought to 60°C and is kept at this temperature for 48h. The resulting mixture is poured into ice-cold water. The precipitate is filtrated and dried under vacuum to obtain 5.1 g of the desired product.

3.115.2. Step ii): 6-Chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-7-nitro-4H-benzo[1,4]oxazin-3-one

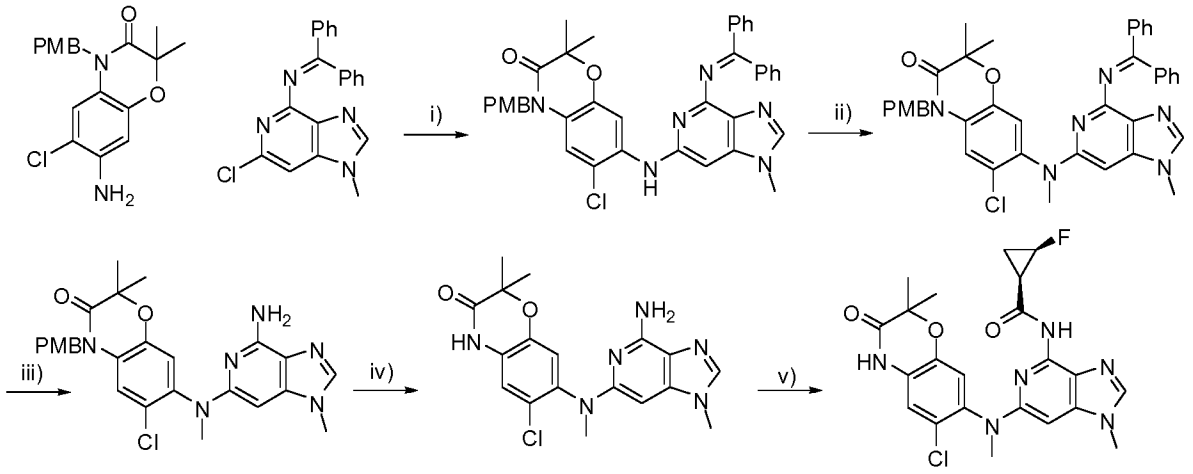
[0655] To the nitroaryl (1.0 eq, 2 g) and Cs_2CO_3 (1.5 eq, 3.81 g) in dry DMF (40 mL) is added PMB chloride (1.0 eq, 1.06 mL). The mixture is stirred at room temperature for 15h. The resulting mixture is concentrated and the residue is stirred in water (15 mL) and pentanes (8 mL). The solid is filtrated and dried under vacuum to obtain 3.39 g of the desired product.

3.115.3. Step iii): 7-Amino-6-chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one

[0656] To the nitroaryl (1.0 eq, 1.5 g) and NH_4Cl (1.5 eq, 319 mg) in THF (5 mL), EtOH (5 mL) and water (2 mL) is added iron powder (5.0 eq, 1.11 g). The suspension is heated at 90°C for 1h. MeOH is

added and the resulting mixture is filtrated through celite. The filtrat is concentrated and the residue is stirred in water. The solid is filtrated and dried under vacuum to obtain 1.04 g of the desired product.

3.116. Compound 104: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {1-methyl-6-[methyl-(2,2,6-trimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-amino]-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.116.1. Step i): 7-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino]-6-chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one

[0657] A degassed mixture of the amine (1.0 eq, 500 mg), the chloroaryl (1.0 eq, 500 mg), $Pd(OAc)_2$ (0.2 eq, 65 mg), BINAP (0.3 eq, 269 mg) and Cs_2CO_3 (2.5 eq, 1.17 g) in dry dioxane (6 mL) in a sealed tube is heated at 110 °C for 1h. The resulting mixture is diluted in EtOAc and water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, the crude is used as such in the following step.

3.116.2. Step ii): 7-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-6-chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one

[0658] To the crude amine (1.0 eq, 1.44 mmol) in dry THF (14 mL) is added NaH (1.5 eq, 86.4 mg). After 5 min, MeI (3.0 eq, 134 µL) is added and the mixture is stirred at room temperature for 2 h. The resulting mixture is diluted with EtOAc and at 0°C is quenched with water. The aqueous is further extracted with EtOAc, the combined organics is dried and concentrated, and the crude is used as such in the following step.

3.116.3. Step iii): 7-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-chloro-4-(4-methoxy-benzyl)-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one

[0659] To a solution of the crude benzophenonimine in THF (3 mL) is added aq. 2M HCl solution (3 mL) and the mixture is stirred at room temperature for 2h. The resulting mixture is extracted with EtOAc, the aqueous is basified using aq. 1M NaOH and extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is purified by silica chromatography (EtOAc: MeOH; 1:0 to 98:2 to 95:5) to give the desired product.

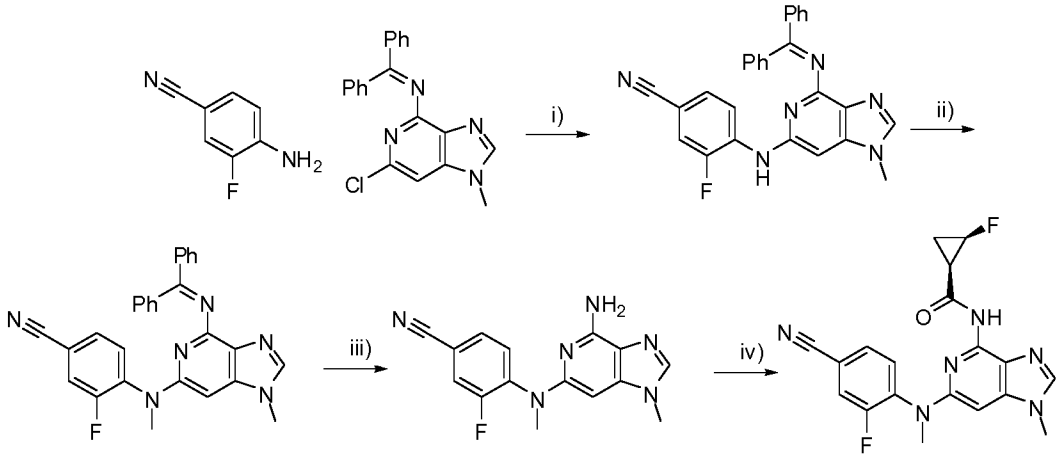
3.116.4. Step iv): 7-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-chloro-2,2-dimethyl-4H-benzo[1,4]oxazin-3-one

[0660] The crude amine is dissolved in TFA (2 mL) and stirred at 120°C for 1h under microwave irradiation (absorption level: normal). The resulting mixture is diluted with EtOAc, quenched with aq. sat. $NaHCO_3$, the aqueous is extracted with EtOAc (3x). The organics are dried and concentrated, and the crude is used as such in the following step.

3.116.5. Step v): (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {1-methyl-6-[methyl-(2,2,6-trimethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-amino]-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0661] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3 eq, 152 mg) in dry DCM (5 mL) at 0 °C is added oxalyl chloride (2.9 eq, 121 µL) followed by 1 drop of DMF. After 30 min, a suspension of the amine (1 eq, 0.487 mmol) in dry DCM (5 mL) is added dropwise, followed by pyridine (4 eq, 0.20 mL), and the mixture is stirred at 0°C for 2h, then warm up to room temperature overnight. The crude mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. The residue is purified by preparative HPLC.

3.117. Compound 105: (1R,2R)-N-[6-(4-cyano-2-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.118. Step i: 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-fluoro-benzonitrile

[0662] Prepared following step ii*)* of compound 47 starting from Benzhydrylidene-(6-chloro-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amine (0.5g, 1eq) and 4-amino-3-fluoro-benzonitrile (0.22g, 1.1 eq).

3.118.1. Step ii: 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-fluoro-benzonitrile

[0663] Prepared following step iii*)* of compound 47 starting from 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-fluoro-benzonitrile.

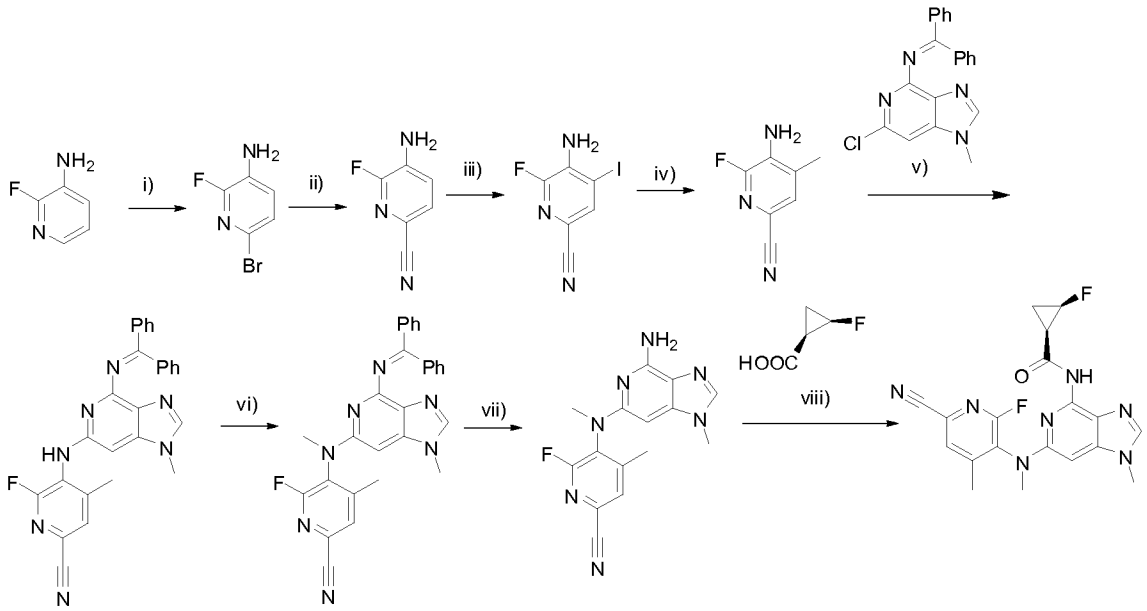
3.118.2. Step iii: 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-fluoro-benzonitrile

[0664] Prepared following step iv) of compound 47 starting from 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-fluoro-benzonitrile.

3.118.3. Step iv: (1R,2R)-N-[6-(4-cyano-2-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0665] Prepared following step v) of compound **47** starting from 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-fluoro-benzonitrile.

3.119. Compound 106: ((1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide)



3.119.1. Step i): 6-bromo-2-fluoro-pyridin-3-amine

[0666] A mixture of 2-fluoropyridin-3-amine (44.6 mmol) and KOAc (44.6 mmol) in AcOH is stirred at room temperature for 1 h. The mixture is cooled to 0 C and BR^2 (44.6 mmol) is added dropwise. The mixture is stirred at 0°C for 15 min. The mixture is concentrated and the residue is dissolved in EtOAc/MeOH. The organic solution is washed (sat. $NaHCO_3$, sat. $Na_2S_2O_3$), dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 100:0 to 80:20 petroleum ether/EtOAc) to yield the desired product.

3.119.2. Step ii): 5-amino-6-fluoro-pyridine-2-carbonitrile

[0667] Prepared accordingly to what reported for the synthesis of compound 96, step ii), using 6-bromo-2-fluoro-pyridin-3-ylamine as starting material.

3.119.3. Step iii): 5-amino-6-fluoro-4-iodo-pyridine-2-carbonitrile

[0668] A mixture of 5-amino-6-fluoro-pyridine-2-carbonitrile (3.62 mmol), I2 (14.5 mmol) and Ag_2SO_4 (14.5 mmol) in EtOH (200 mL) is stirred at 70°C for 16 h. 5 more equivalents of I2 and Ag_2SO_4 are added and the reaction is stirred at 70°C for a further 72 h. The mixture is filtered, concentrated and

purified by flash column chromatography (SiO_2, 20:80 to 40:60 EtOAc/cyclohexane) to yield the desired product.

3.119.4. Step iv): 5-amino-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0669] A mixture of 5-amino-6-fluoro-4-iodo-pyridine-2-carbonitrile (3 mmol), methyl boronic acid (9.1 mmol), $Pd(dppf)CL_2$.DCM (0.32 mmol) and Cs_2CO_3 (15.2 mmol) in 1,4-dioxane (8 mL) is stirred at 105°C for 5 h. The mixture is diluted (EtOAc), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 10:90 to 50:50 EtOAc/petroleum ether) to yield the desired product.

3.119.5. Step v): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0670] A mixture of N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine (2.88 mmol), 5-amino-6-fluoro-4-methyl-pyridine-2-carbonitrile (2.64 mmol), $Pd(OAc)_2$ (0.58 mmol), BINAP (0.864 mmol) and Cs_2CO_3 (13 mmol) in 1,4-dioxane is stirred in a sealed tube at 110 C for 1 h. The mixture is cooled to room temperature and a further 0.288 mmol of $Pd(OAc)_2$ and 0.43 mmol of BINAP are added. The mixture is stirred at 110°C for a further 2 h. The mixture is diluted (EtOAc), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated. The mixture is triturated with EtOAc/Et_2O and filtered off to afford the desired product.

3.119.6. Step vi): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0671] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile as starting material.

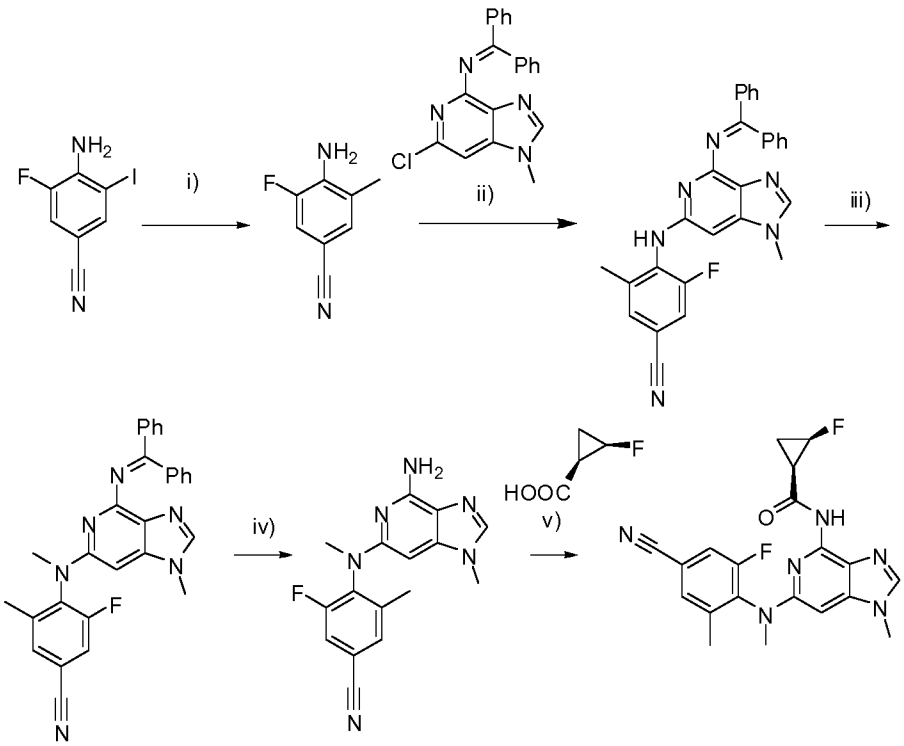
3.119.7. Step vii): 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile

[0672] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile as starting material.

3.119.8. Step viii): (1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0673] Prepared accordingly to what reported for the synthesis of compound 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-6-fluoro-4-methyl-pyridine-2-carbonitrile **89**, step iv).

3.120. Compound 107: ((1R,2R)-N-[6-(4-cyano-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide)



3.120.1. Step i): 4-amino-3-fluoro-5-methyl-benzonitrile

[0674] Prepared accordingly to what reported for the synthesis of compound 106, step iv), using 4-amino-3-fluoro-benzonitrile as starting material.

3.120.2. Step ii): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-fluoro-5-methyl-benzonitrile

[0675] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 4-amino-3-fluoro-5-methyl-benzonitrile and intermediate 1 as starting materials.

3.120.3. Step iii): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-fluoro-5-methyl-benzonitrile

[0676] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-fluoro-5-methyl-benzonitrile as starting material.

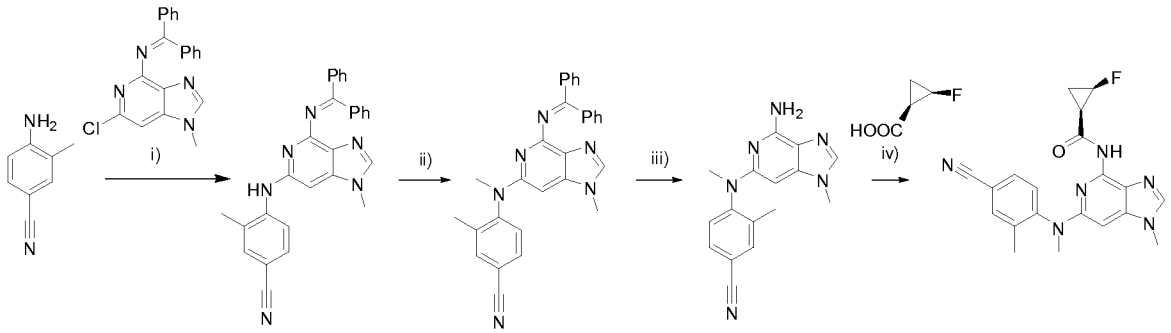
3.120.4. Step iv): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-fluoro-5-methyl-benzonitrile

[0677] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-fluoro-5-methyl-benzonitrile as starting material.

3.120.5. Step v): (1R,2R)-N-[6-(4-cyano-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0678] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-fluoro-5-methyl-benzonitrile as starting material.

3.120.6. Compound 108



3.120.7. Step i): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-methyl-benzonitrile

[0679] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 4-amino-3-methyl-benzonitrile and intermediate 1 as starting materials.

3.120.8. Step ii): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-methyl-benzonitrile

[0680] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-methyl-benzonitrile as starting material.

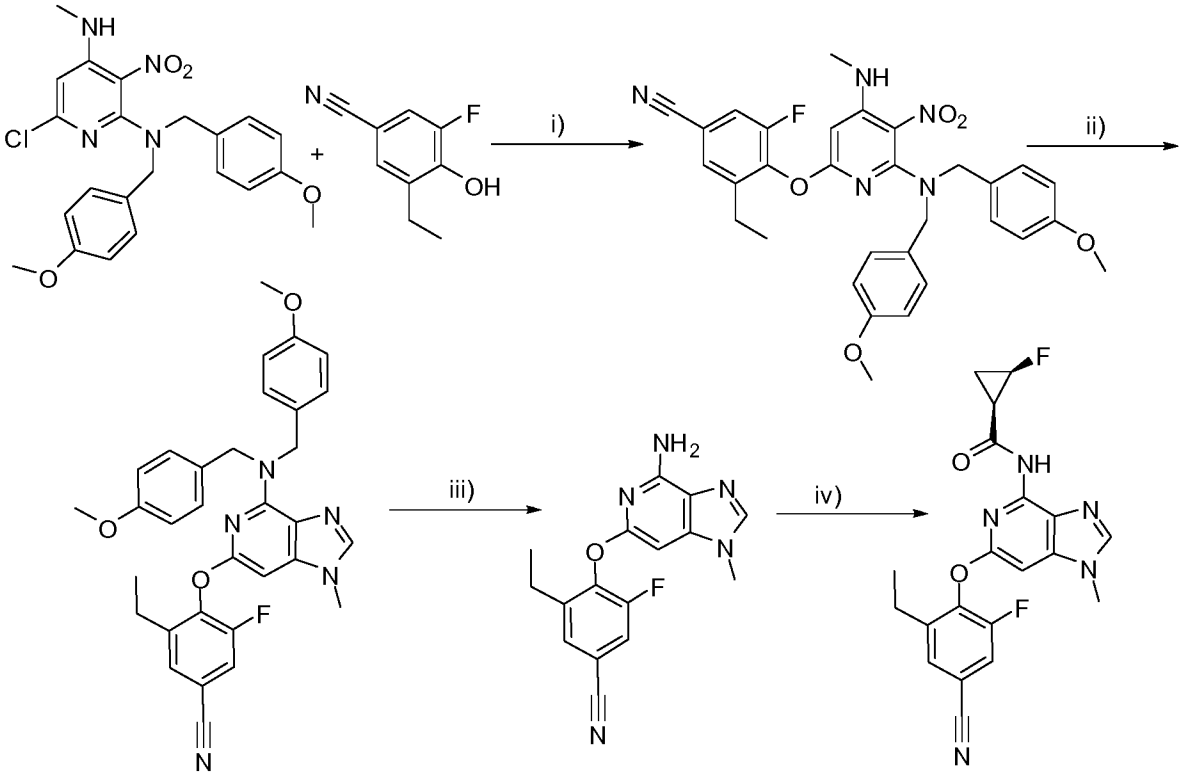
3.120.9. Step iii): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-methyl-benzonitrile

[0681] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-methyl-benzonitrile as starting material.

3.120.10. Step iv): (1R,2R)-N-[6-(4-cyano-N,2-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0682] Prepared accordingly to what reported for the synthesis of compound 89, step iv).

3.121. Compound 109



3.121.1. Step i): 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]oxy]-3-ethyl-5-fluoro-benzonitrile

[0683] Prepared accordingly to what reported for the synthesis of compound 69, step iv), using 6-chloro-N2,N2-bis[(4-methoxyphenyl)methyl]-N4-methyl-3-nitro-pyridine-2,4-diamine and 3-ethyl-5-fluoro-4-hydroxy-benzonitrile as starting materials.

3.121.2. Step ii): 4-[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-3-ethyl-5-fluoro-benzonitrile

[0684] Prepared accordingly to what reported for the synthesis of compound **69**, step iii), using 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]oxy]-3-ethyl-5-fluoro-benzonitrile as starting material.

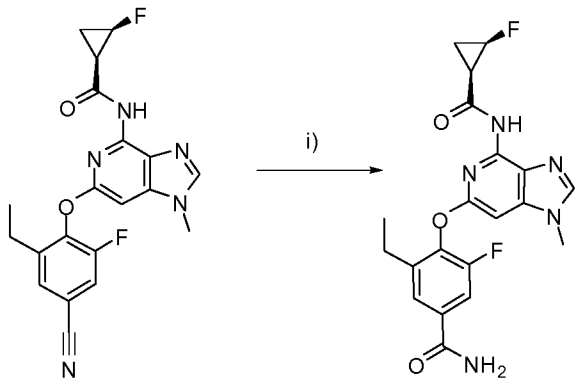
3.121.3. Step iii): 4-(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)oxy-3-ethyl-5-fluoro-benzonitrile

[0685] Prepared accordingly to what reported for the synthesis of compound 69, step vi), using 4-[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-3-ethyl-5-fluoro-benzonitrile as starting material.

3.121.4. Step iv): (1R,2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0686] Prepared accordingly to what reported for the synthesis of compound 69, step vii).

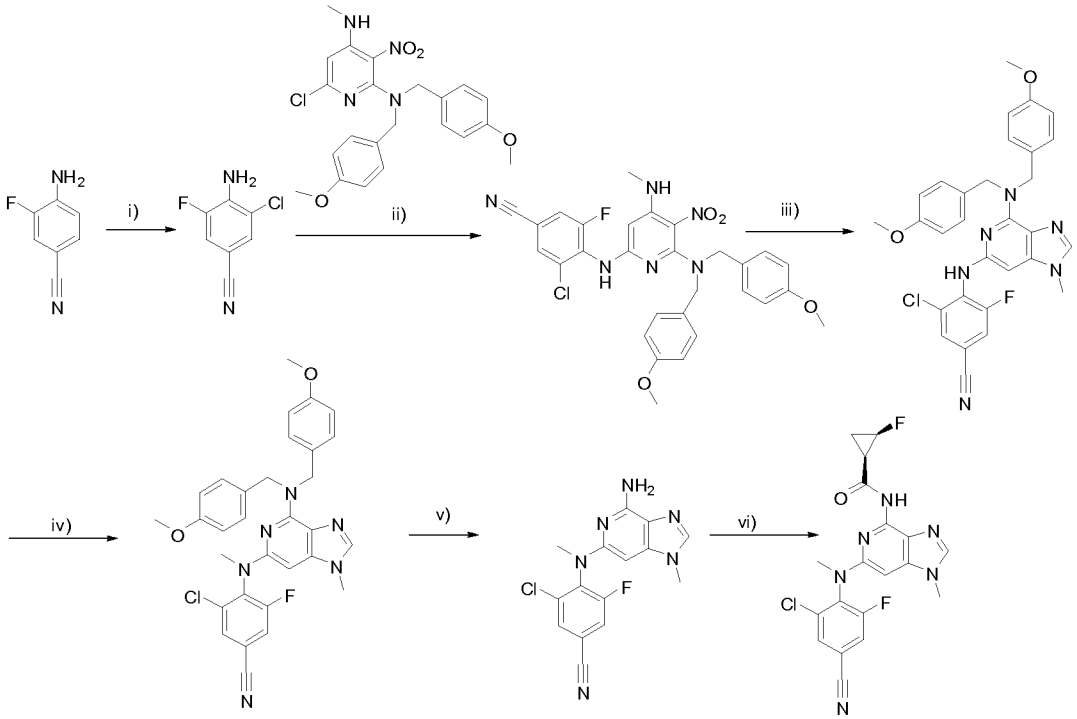
3.122. Compound 110: (3-ethyl-5-fluoro-4-(4-((1R,2R)-2-fluorocyclopropane carboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yloxy)benzamide)



3.122.1. Step i): (3-ethyl-5-fluoro-4-(4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yloxy)benzamide)

[0687] Prepared accordingly to what reported for the synthesis of compound 68, step ii), using (3-ethyl-5-fluoro-4-(4-((1R,2R)-2-fluorocyclopropanecarboxamido)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yloxy)benzamide) as starting material.

3.123. Compound 111: (1R,2R)-N-[6-(2-chloro-4-cyano-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.123.1. Step i): 4-amino-3-chloro-5-fluoro-benzonitrile

[0688] A mixture of 4-amino-3-fluorobenzonitrile (184 mmol) and NCS (276 mmol) in AcOH (300 mL) is stirred at 70°C for approximately 16 h. The mixture is concentrated. H_2O is added to the residue and the solid product is filtered off and washed (sat. $NaHCO_3$ and H_2O). To eliminate H_2O, THF is added and removed under reduced pressure to yield the desired product (Int. 21).

3.123.2. Step ii): 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]amino]-3-chloro-5-fluoro-benzonitrile

[0689] A mixture of 6-chloro-N2,N2-bis[(4-methoxyphenyl)methyl]-N4-methyl-3-nitro-pyridine-2,4-diamine (3.39 mmol), 4-amino-3-chloro-5-fluoro-benzonitrile (6.78 mmol) and Cs_2CO_3 (13.6 mmol) in DMA (15 mL) is stirred for 16 h at 120 °C. A solution of saturated NH_4Cl is added to the mixture. The solid is filtered out and further washed with water. The solid is taken up in EtOAc and the organic mixture is washed (H_2O and brine), dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 100:0 to 50:50 petroleum ether/EtOAc) to afford the desired product.

3.123.3. Step iii): 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-chloro-5-fluoro-benzonitrile

[0690] A mixture of 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]amino]-3-chloro-5-fluoro-benzonitrile (1.39 mmol), Zn (13.9 mmol), NH_4Cl (catalytic amount), $TsOH.H_2O$ (4.17 mmol) in 3:2 $HCO(OMe)_3$/MeOH (14 mL) is stirred at 40 °C for 1 h. The mixture is filtered off and concentrated. The residue is dissolved in $HCO(OMe)_3$ and the mixture is stirred at 40 °C for 1 h, at 80 °C for 3 h and at rt for 16 h. The mixture is concentrated and the residue is taken up in DCM/MeOH. The organic mixture is washed (sat. $NaHCO_3$), dried (filtered through a phase separator) and concentrated to afford the desired product.

3.123.4. Step iv): 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-chloro-5-fluoro-benzonitrile

[0691] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-chloro-5-fluoro-benzonitrile as starting material.

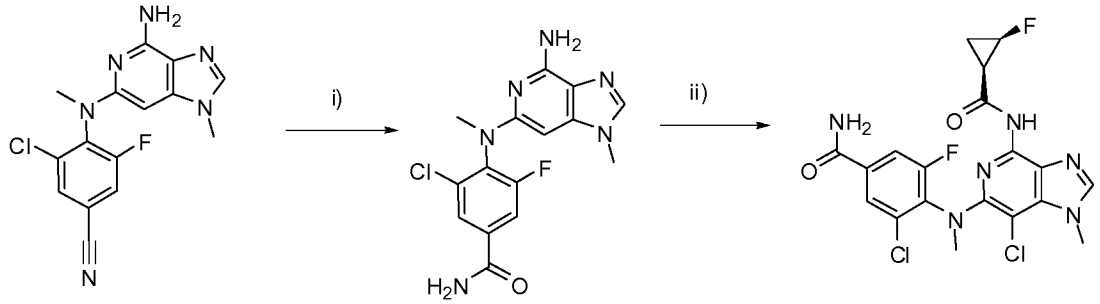
3.123.5. Step v): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-5-fluoro-benzonitrile

[0692] Prepared accordingly to what reported for the synthesis of compound 69, step vi) , using 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-chloro-5-fluoro-benzonitrile as starting material.

3.123.6. Step vi): (1R,2R)-N-[6-(2-chloro-4-cyano-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0693] Prepared accordingly to what reported for the synthesis of compound compound 69, step vii) , using 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-5-fluoro-benzonitrile as starting material.

3.124. Compound 112: (3-chloro-4-[[7-chloro-4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-5-fluoro-benzamide)



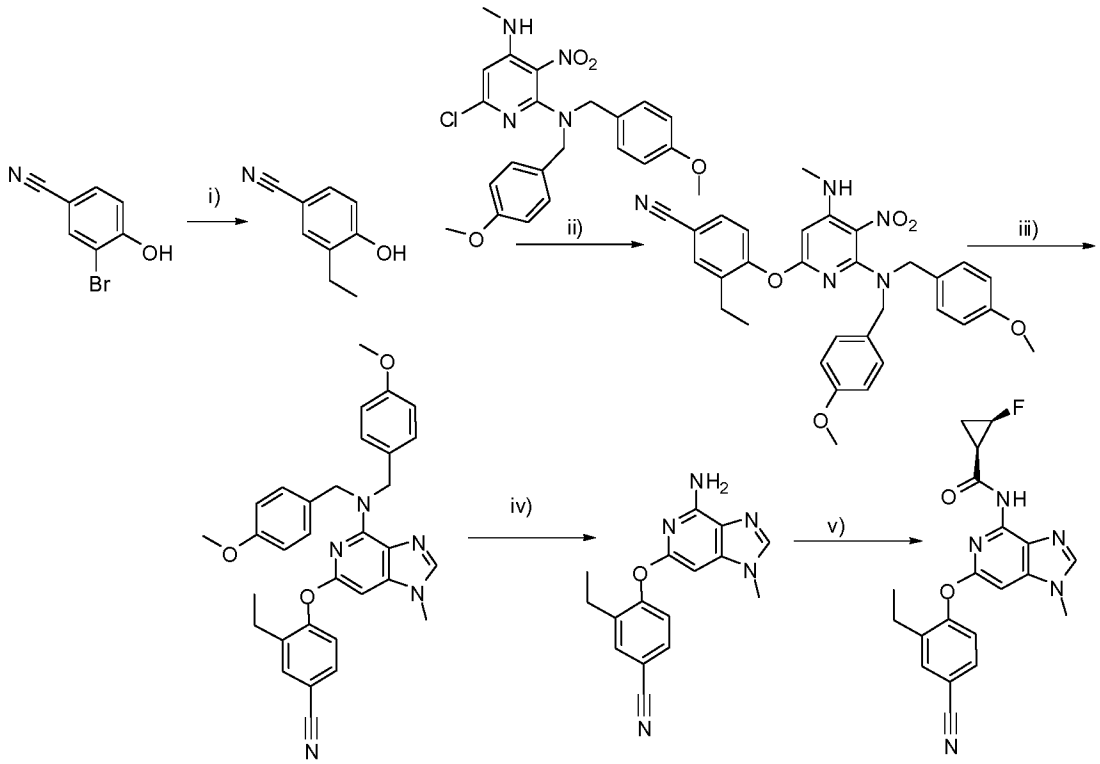
3.124.1. Step i): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-5-fluoro-benzamide

[0694] A mixture of 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-5-fluoro-benzonitrile (0.172 mmol), 1 N NaOH (0.4 mL), H_2O_2 35% in H_2O (0.25 mL) in 4:1 EtOH/DMSO (1 mL) is stirred at 50 °C for 1 h. The mixture is concentrated and the residue is partitioned between DCM and sat. $NaHCO_3$. The phases are separated and the organic layer is dried (filtered through phase separator) and concentrated to afford the desired product.

3.124.2. Step ii): (3-chloro-4-[[7-chloro-4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-5-fluoro-benzamide)

[0695] Oxalyl chloride (0.241 mmol) is added to a solution of (R,R)-2-fluoro-cyclopropanecarboxylic acid (0.258 mmol) in DCM (1 mL) at 0 °C. DMF (1 drop) is added. The mixture is stirred for 30 min at 0 °C. A suspension of 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-5-fluoro-benzamide (0.172 mmol) and pyridine (0.52 mmol) in DCM (1 mL) is added. The mixture is stirred for 1 h at room temperature. LCMS analysis revealed that the title compound is unexpectedly formed. The reaction mixture is quenched with sat. $NaHCO_3$ and the mixture is diluted with DCM. The two phases are separated and the organic layer is dried (filtered through phase separator) and concentrated. The residue is purified by preparatory HPLC to afford the title compound.

3.125. Compound 113: (1R,2R)-N-[6-(4-cyano-2-ethyl-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.125.1. Step i): 3-ethyl-4-hydroxy-benzonitrile

[0696] $PdCl_2dppf$ (0.63 mmol) and Cs_2CO_3 (25.2 mmol) are dissolved in anhydrous THF (25 mL) and the suspension is degassed under nitrogen atmosphere. 3-bromo-4-hydroxy-benzonitrile, (12.6 mmol) and triethylborane (1M in hexane, 25.2 mmol) are added and the reaction is refluxed for 1.5 h, using a condenser. The mixture is concentrated. The residue is partitioned between 1 M NaOH and EtOAc. The two phases are separated and the aqueous layer is acidified (conc. HCl) and extracted (DCM). The organic layer is dried (filtered through phase separator) and concentrated to afford the desired product.

3.125.2. Step ii): 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]oxy]-3-ethyl-benzonitrile

[0697] Prepared accordingly to what reported for the synthesis of compound 69, step iv), using 6-chloro-N2,N2-bis[(4-methoxyphenyl)methyl]-N4-methyl-3-nitro-pyridine-2,4-diamine and 3-ethyl-4-hydroxy-benzonitrile as starting materials.

3.125.3. Step iii): 4-[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-3-ethyl-benzonitrile

[0698] Prepared accordingly to what reported for the synthesis of compound **111**, step iii), using 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]oxy]-3-ethyl-benzonitrile as starting material.

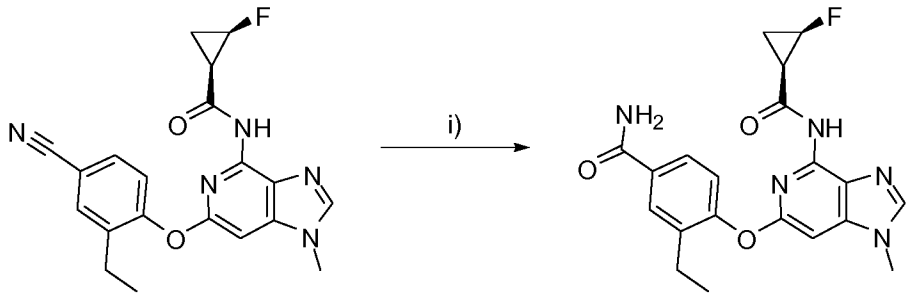
3.125.4. Step iv): 4-(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)oxy-3-ethyl-benzonitrile

[0699] Prepared accordingly to what reported for the synthesis of compound 69, step vi), using 4-[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-3-ethyl-benzonitrile as starting material.

3.125.5. Step v): (1R,2R)-N-[6-(4-cyano-2-ethyl-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

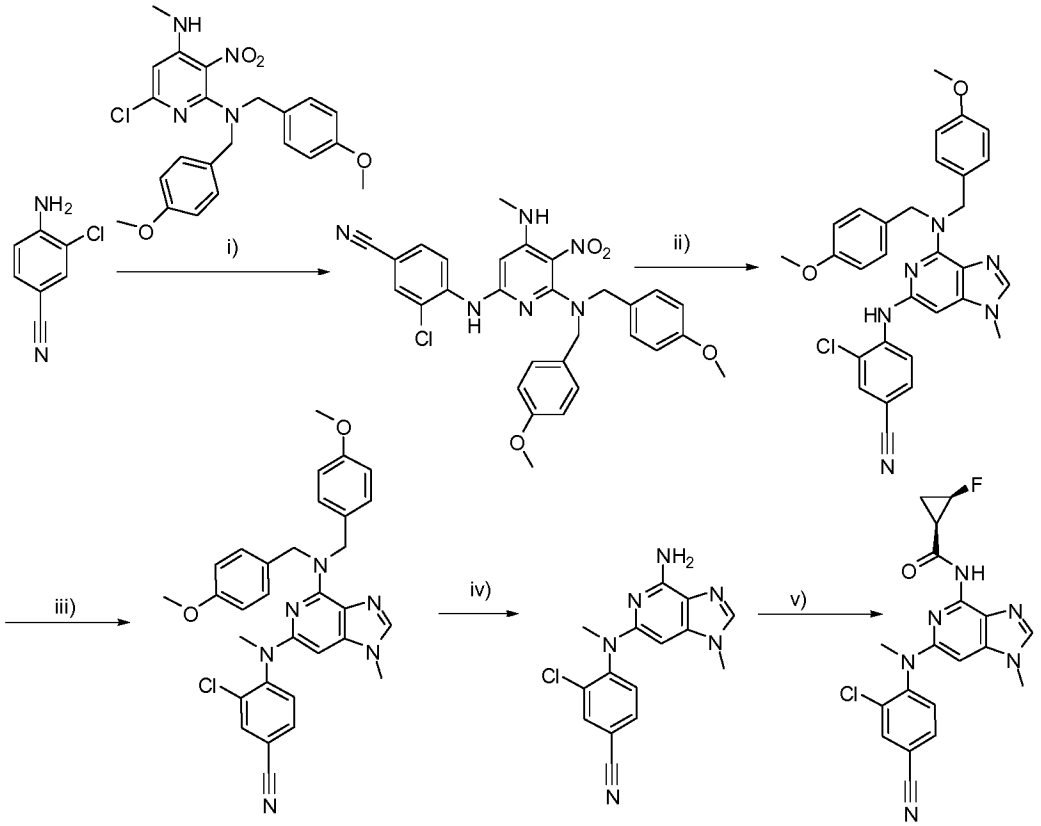
[0700] Prepared accordingly to what reported for the synthesis of compound compound 69, step vii).

3.126. Compound 114: 3-ethyl-4-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-benzamide



[0701] Prepared accordingly to what reported for the synthesis of compound 68, step ii), using (1R,2R)-N-[6-(4-cyano-2-ethyl-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide as starting material.

3.127. Compound 115: (1R,2R)-N-[6-(2-chloro-4-cyano-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.127.1. Step i): 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]amino]-3-chloro-benzonitrile

[0702] Prepared accordingly to what reported for the synthesis of compound 111, step ii), using 4-amino-3-chlorobenzonitrile as starting material.

3.127.2. Step ii): 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-chloro-benzonitrile

[0703] Prepared accordingly to what reported for the synthesis of compound 111, step iii), using 4-[[6-[bis[(4-methoxyphenyl)methyl]amino]-4-(methylamino)-5-nitro-2-pyridyl]amino]-3-chloro-benzonitrile as starting material.

3.127.3. Step iii): 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-chloro-benzonitrile

[0704] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-3-chloro-benzonitrile as starting material.

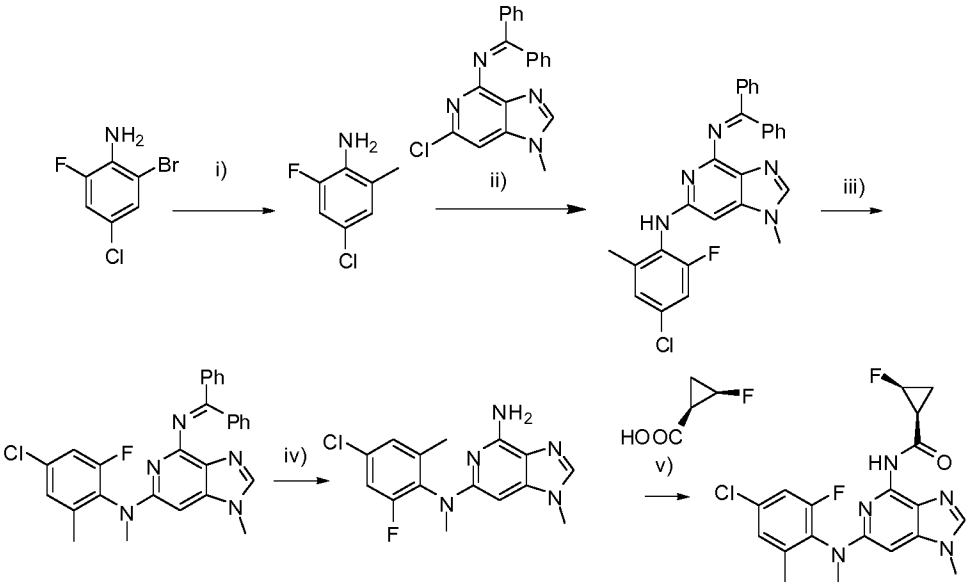
3.127.4. Step iv): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-benzonitrile

[0705] Prepared accordingly to what reported for the synthesis of compound 69, step vi) , using 4-[[4-[bis[(4-methoxyphenyl)methyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-chloro-benzonitrile as starting material.

3.127.5. Step v): (1R,2R)-N-[6-(2-chloro-4-cyano-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0706] Prepared accordingly to what reported for the synthesis of compound 69, step vii) , using 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-3-chloro-benzonitrile as starting material.

3.128. Compound 116: (1R,2R)-N-[6-(4-chloro-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.128.1. Step i): 4-chloro-2-fluoro-6-methyl-aniline

[0707] A mixture of 2-bromo-4-chloro-6-fluoro-benzenamine (8.91 mmol), trimethylboroxine (9.36 mmol), Pd(dppf)Cl_2.DCM (0.891 mmol) and K_2CO_3 (26.7 mmol) in 10:1 1,4-dioxane/H_2O (44 mL) is stirred at 110°C for 16 h. The mixture is concentrated and the residue is taken up in DCM. The solids are filtered off and the filtrated is concentrated. The residue is purified by flash column chromatography (SiO_2, 0:100 to 20:80 EtOAc/petroleum ether) to yield the desired product.

3.128.2. Step ii): 4-(benzhydrylideneamino)-N-(4-chloro-2-fluoro-6-methyl-phenyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine

[0708] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 4-chloro-2-fluoro-6-methyl-aniline and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.128.3. Step iii): 4-(benzhydrylideneamino)-N-(4-chloro-2-fluoro-6-methyl-phenyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine

[0709] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-(benzhydrylideneamino)-N-(4-chloro-2-fluoro-6-methyl-phenyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine as starting material.

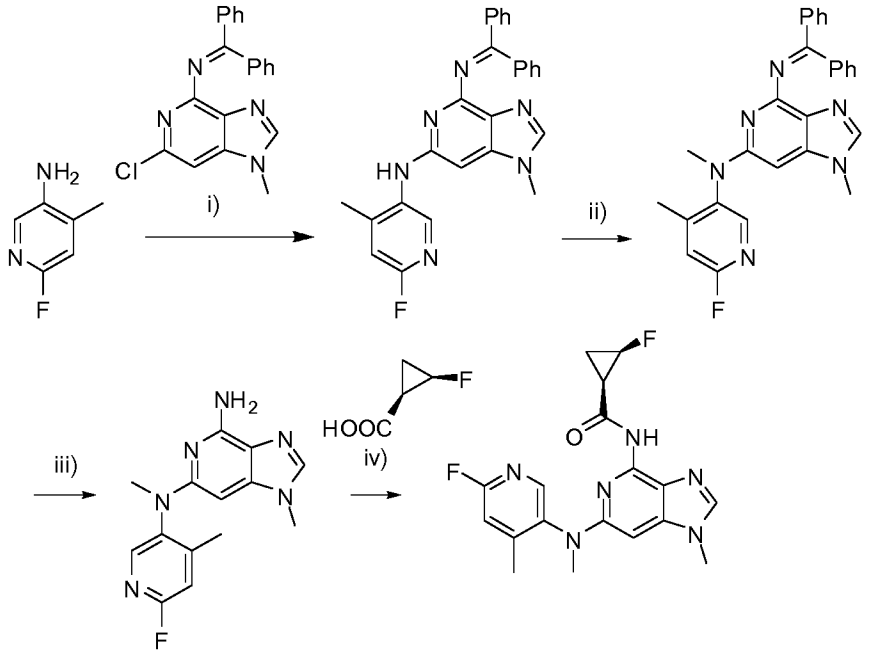
3.128.4. Step iv): N6-(4-chloro-2-fluoro-6-methyl-phenyl)-N6,1-dimethyl-imidazo[4,5-c]pyridine-4,6-diamine

[0710] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 4-(benzhydrylideneamino)-N-(4-chloro-2-fluoro-6-methyl-phenyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine as starting material.

3.128.5. Step v): (1R,2R)-N-[6-(4-chloro-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0711] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using N6-(4-chloro-2-fluoro-6-methyl-phenyl)-N6,1-dimethyl-imidazo[4,5-c]pyridine-4,6-diamine as starting material.

3.129. Compound 117: (1R,2R)-2-fluoro-N-[6-[(6-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide



3.129.1. Step i): 4-(benzhydrylideneamino)-N-(6-fluoro-4-methyl-3-pyridyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine

[0712] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 6-fluoro-4-methyl-3-pyridinamine and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.129.2. Step ii): 4-(benzhydrylideneamino)-N-(6-fluoro-4-methyl-3-pyridyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine

[0713] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-(benzhydrylideneamino)-N-(6-fluoro-4-methyl-3-pyridyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine as starting material.

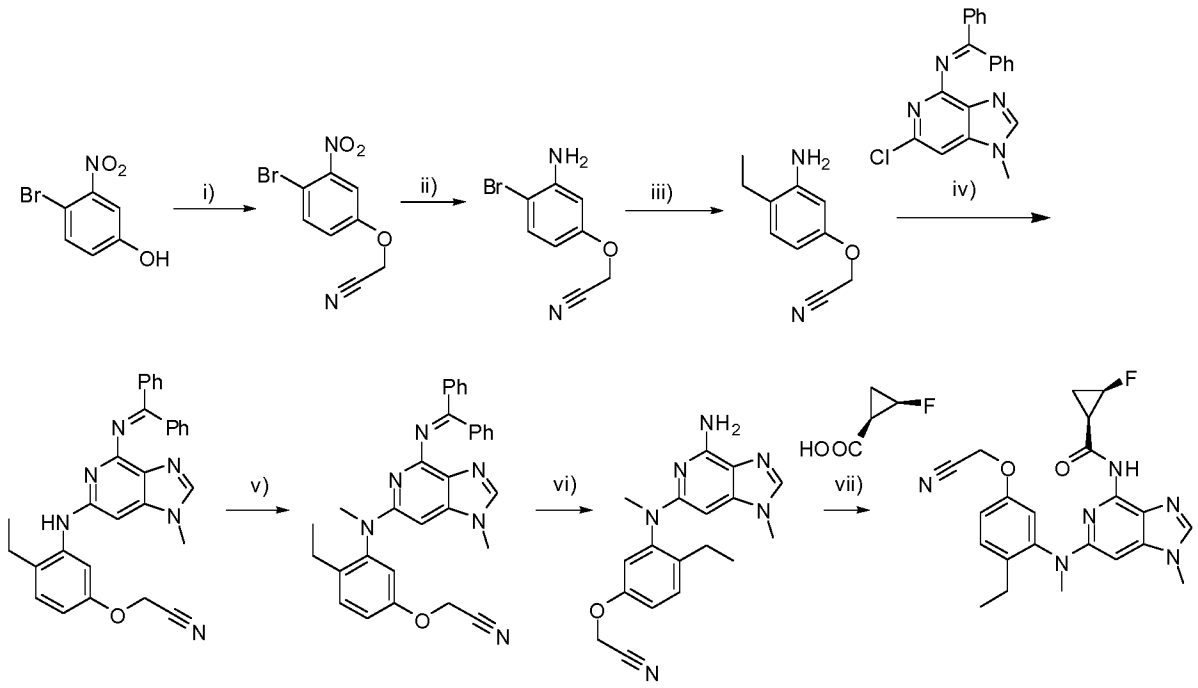
3.129.3. Step iii): N6-(6-fluoro-4-methyl-3-pyridyl)-N6,1-dimethyl-imidazo[4,5-c]pyridine-4,6-diamine

[0714] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 4-(benzhydrylideneamino)-N-(6-fluoro-4-methyl-3-pyridyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine as starting material.

3.129.4. Step iv): (1R,2R)-2-fluoro-N-[6-[(6-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide

[0715] Prepared accordingly to what reported for the synthesis of compound 89, step iv).

3.130. Compound 118: (1R,2R)-N-[6-[5-(cyanomethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.130.1. Step i): 2-(4-bromo-3-nitro-phenoxy)acetonitrile

[0716] Bromoacetonitrile (11.5 mmol) is added to a mixture of 4-bromo-3-nitrophenol (9.22 mmol) and K_2CO_3 in CH_3CN (15 mL). The mixture is stirred for 1.5 h. The mixture is concentrated and the residue is partitioned between DCM and sat. $NaHCO_3$. The two phases are separated and the organic layer is dried (filtered through phase separator) and concentrated to afford the desired product.

3.130.2. Step ii): 2-(3-amino-4-bromo-phenoxy)acetonitrile

[0717] HCOOH (7.5 mL) is added to a mixture of 2-(4-bromo-3-nitro-phenoxy)acetonitrile (9.22 mmol), Zn (92.2 mmol) and NH_4Cl (catalytical amount) in MeOH (40 mL) at 0 °C. The mixture is stirred at room temperature for 10 min and at 50 °C for 30 min. The mixture is filtered and the filtrate is concentrated. The residue is partitioned between DCM and sat. $NaHCO_3$. The two phases are separated and the organic layer is dried (filtered through phase separator) and concentrated. The residue is purified by flash column chromatography (SiO_2, 98:2 to 50:50 petroleum ether/EtOAc) to afford the desired product.

3.130.3. Step iii): 2-(3-amino-4-ethyl-phenoxy)acetonitrile

[0718] A mixture of $PdCl_2dppf$ (0.771 mmol) and Cs_2CO_3 (46.3mmol) in DMF (23 mL) is degassed under nitrogen atmosphere. H_2O (0.3 mL) is added followed by triethylborane (1M in THF, 11.6 mmol) and a solution of 2-(3-amino-4-bromo-phenoxy)acetonitrile (7.71 mmol) in DMF (7 mL). The mixture is stirred at 60 °C for 30 min. The mixture is concentrated and the residue is taken up in EtOAc. The organic mixture is washed (sat. $NaHCO_3$ and H_2O) dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 95:5 to 50:50 petroleum ether/EtOAc) to afford the desired product.

3.130.4. Step iv): 2-[3-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-ethyl-phenoxy]acetonitrile

[0719] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 2-(3-amino-4-ethyl-phenoxy)acetonitrile and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.130.5. Step v): 2-[3-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-ethyl-phenoxy]acetonitrile

[0720] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 2-[3-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-ethyl-phenoxy]acetonitrile as starting material.

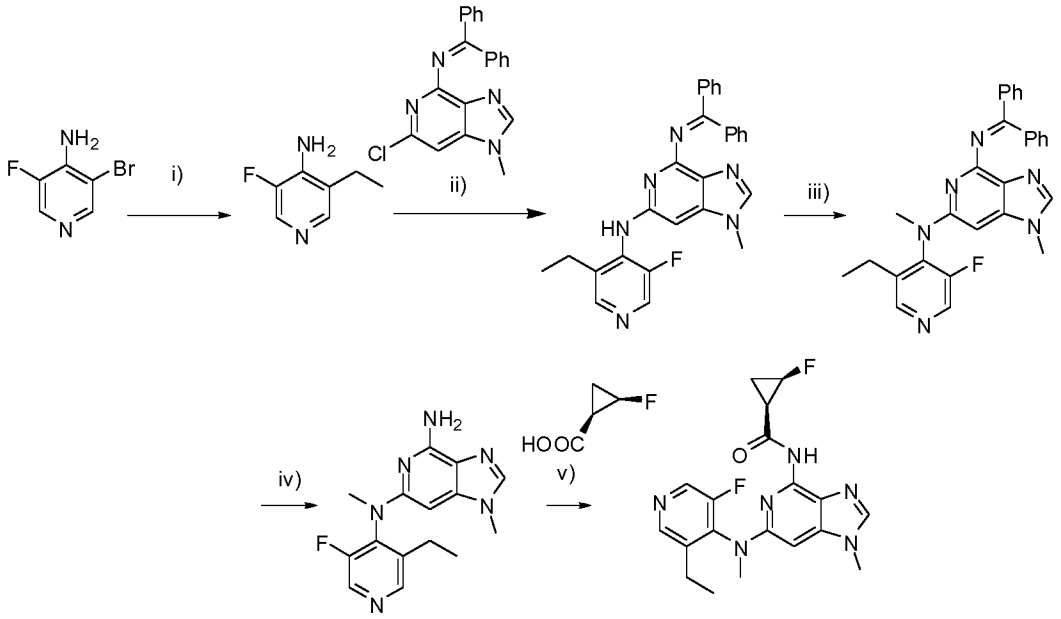
3.130.6. Step vi): 2-[3-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-ethyl-phenoxy]acetonitrile

[0721] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 2-[3-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-ethyl-phenoxy]acetonitrile as starting material.

3.130.7. Step vii): (1R,2R)-N-[6-[5-(cyanomethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0722] Prepared accordingly to what reported for the synthesis of compound 89, step iv).

3.131. Compound 119: (1R,2R)-N-[6-[(3-ethyl-5-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.131.1. Step i): 3-ethyl-5-fluoro-pyridin-4-amine

[0723] Prepared accordingly to what reported for the synthesis of compound 118, step ii), using 3-bromo-5-fluoropyridin-4-amine as starting material.

3.131.2. Step ii): 4-(benzhydrylideneamino)-N-(3-ethyl-5-fluoro-4-pyridyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine

[0724] Prepared accordingly to what reported for the synthesis of compound 89, step i), using 3-ethyl-5-fluoro-pyridin-4-amine and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.131.3. Step iii): 4-(benzhydrylideneamino)-N-(3-ethyl-5-fluoro-4-pyridyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine

[0725] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-(benzhydrylideneamino)-N-(3-ethyl-5-fluoro-4-pyridyl)-1-methyl-imidazo[4,5-c]pyridin-6-amine as starting material.

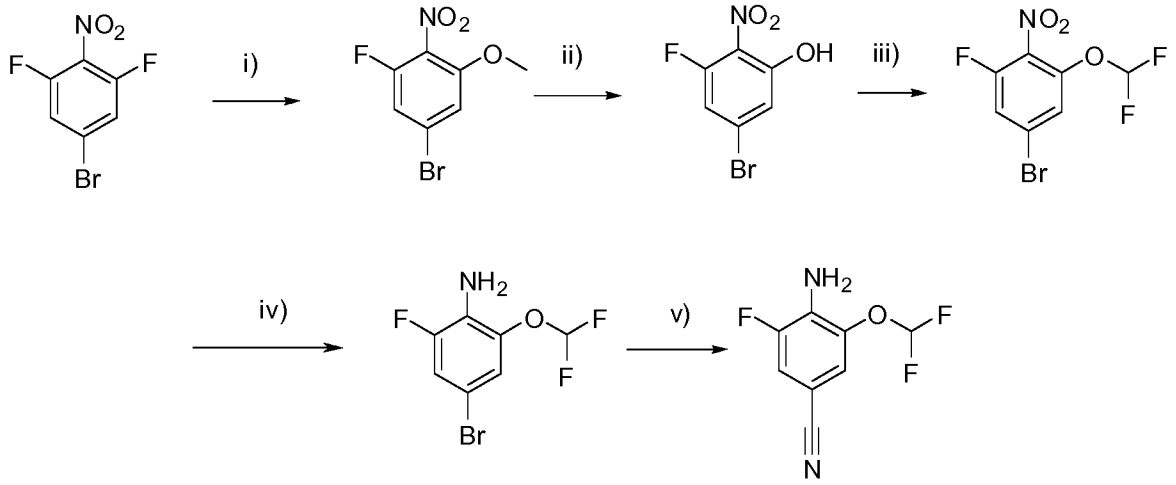
3.131.4. Step iv): N6-(3-ethyl-5-fluoro-4-pyridyl)-N6,1-dimethyl-imidazo[4,5-c]pyridine-4,6-diamine

[0726] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 4-(benzhydrylideneamino)-N-(3-ethyl-5-fluoro-4-pyridyl)-N,1-dimethyl-imidazo[4,5-c]pyridin-6-amine as starting material.

3.131.5. Step v): (1R,2R)-N-[6-[(3-ethyl-5-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0727] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using N6-(3-ethyl-5-fluoro-4-pyridyl)-N6,1-dimethyl-imidazo[4,5-c]pyridine-4,6-diamine as starting material.

3.132. Intermediate 28: 4-amino-3-(difluoromethoxy)-5-fluoro-benzonitrile



3.132.1. Step i): 5-Bromo-1-fluoro-3-methoxy-2-nitro-benzene

[0728] 5-Bromo-1,3-difluoro-2-nitro-benzene (4.2 mmol) is dissolved in MeOH (8 mL) and KOH (4.62 mmol) is added. The reaction mixture is stirred at reflux for 3h. The reaction mixture is dilluted with water (20ml) and extracted with DCM (3 x 30ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure to afford the desired product.

3.132.2. Step ii): 5-Bromo-3-fluoro-2-nitro-phenol

[0729] 5-Bromo-1-fluoro-3-methoxy-2-nitro-benzene (3.78 mmol) is dissolved in dry DCM (4 mL) and cooled to 0°C. Boron tribromide (1 M in DCM, 5.67 mmol) is added and reaction mixture is allowed to warm to room temperature and stirred for 1 h. Reaction mixture is diluted with water (20ml) and extracted with DCM (3 x 20ml). Organic layers are combined, passed through phase separator and concentrated. The residue is purified by flash column chromatography (SiO_2, 100:0 to 50:50 cyclohexane/EtOAc) to afford the desired product.

3.132.3. Step iii): 5-Bromo-1-difluoromethoxy-3-fluoro-2-nitro-benzene

[0730] Prepared accordingly to what reported for the synthesis of intermediate 16, step i), using 5-Bromo-3-fluoro-2-nitro-phenol as starting material.

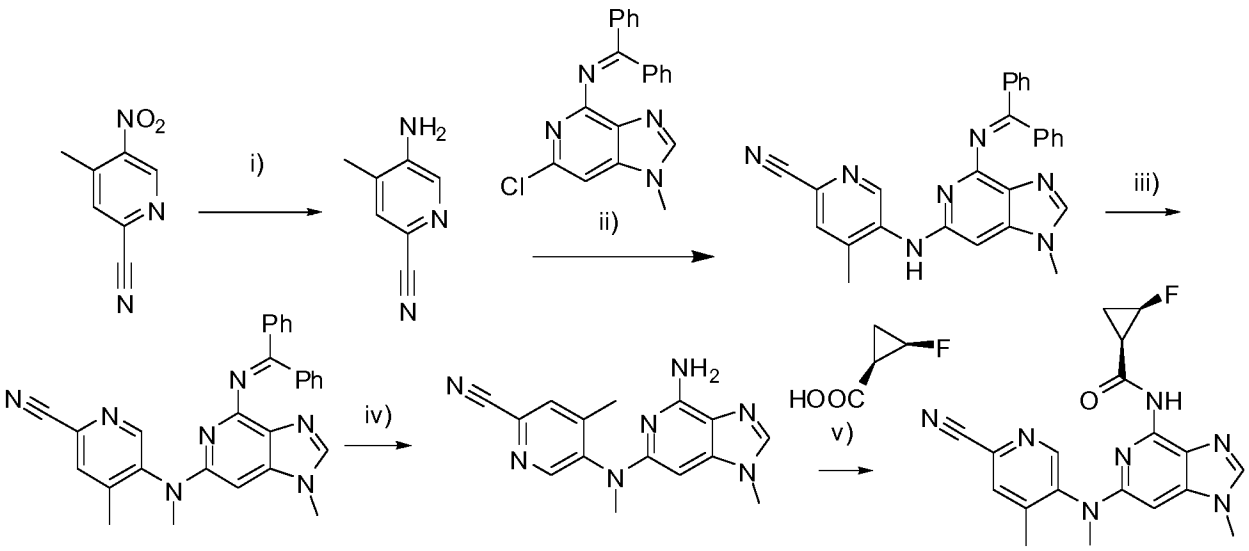
3.132.4. Step iv): 4-Bromo-2-difluoromethoxy-6-fluoro-phenylamine

[0731] 5-Bromo-1-difluoromethoxy-3-fluoro-2-nitro-benzene (4.96 mmol) is dissolved in mixture of THF (25ml) and MeOH (25ml). Zinc dust (50) and ammonium chloride (50 mmol) are added and the resulting mixture is stirred at 60°C for 2 h. Reaction mixture is cooled to room temperature, filtered, diluted with water (30ml) and extracted with DCM (3 x 30ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure to afford the desired product.

3.132.5. Step v): 4-Amino-3-(difluoromethoxy)-5-fluoro-benzonitrile

[0732] 4-Bromo-2-difluoromethoxy-6-fluoro-phenylamine(2.48 mmol) and zinc cyanide (1.80 mmol) are dissolved in a mixture of DMF (20ml) and DMA (10ml), heated to 90°C and bubbled with argon for 5 min. Then Tetrakis(triphenylphosphine)palladium(0) (0.25 mmol) is added, reaction vessel is sealed and stirred at 90°C for 2h. The reaction mixture is diluted with water (50ml) and extracted with DCM (3 x 50ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure. The residue is purified by flash column chromatography (SiO_2, 100:0 to 0:100 cyclohexane/EtOAc) to afford the desired product.

3.133. Compound 120: (1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide



3.133.1. Step i): 5-amino-4-methyl-pyridine-2-carbonitrile

[0733] To a suspension of 4-methyl-5-nitro-pyridine-2-carbonitrile (12.26 mmol) and ammonium chloride (61.3 mmol) in water (55 mL) is added Zn dust (122.6 mmol) under ice-cooling over 15 min and the mixture is stirred at the same temperature for 1.5 h. To the reaction mixture is added ethyl acetate (55 mL) and the resulting mixture is stirred at room temperature for 2 h. The insoluble material is removed by filtration and the organic layer of the filtrate is separated. The organic layer is washed with brine, dried and the solvent is removed under reduced pressure affording desired product.

3.133.2. Step ii): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-methyl-pyridine-2-carbonitrile

[0734] Prepared accordingly to what reported for the synthesis of compound 67, step i), using 5-amino-4-methyl-pyridine-2-carbonitrile and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.133.3. Step iii): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-methyl-pyridine-2-carbonitrile

[0735] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-methyl-pyridine-2-carbonitrile as starting material.

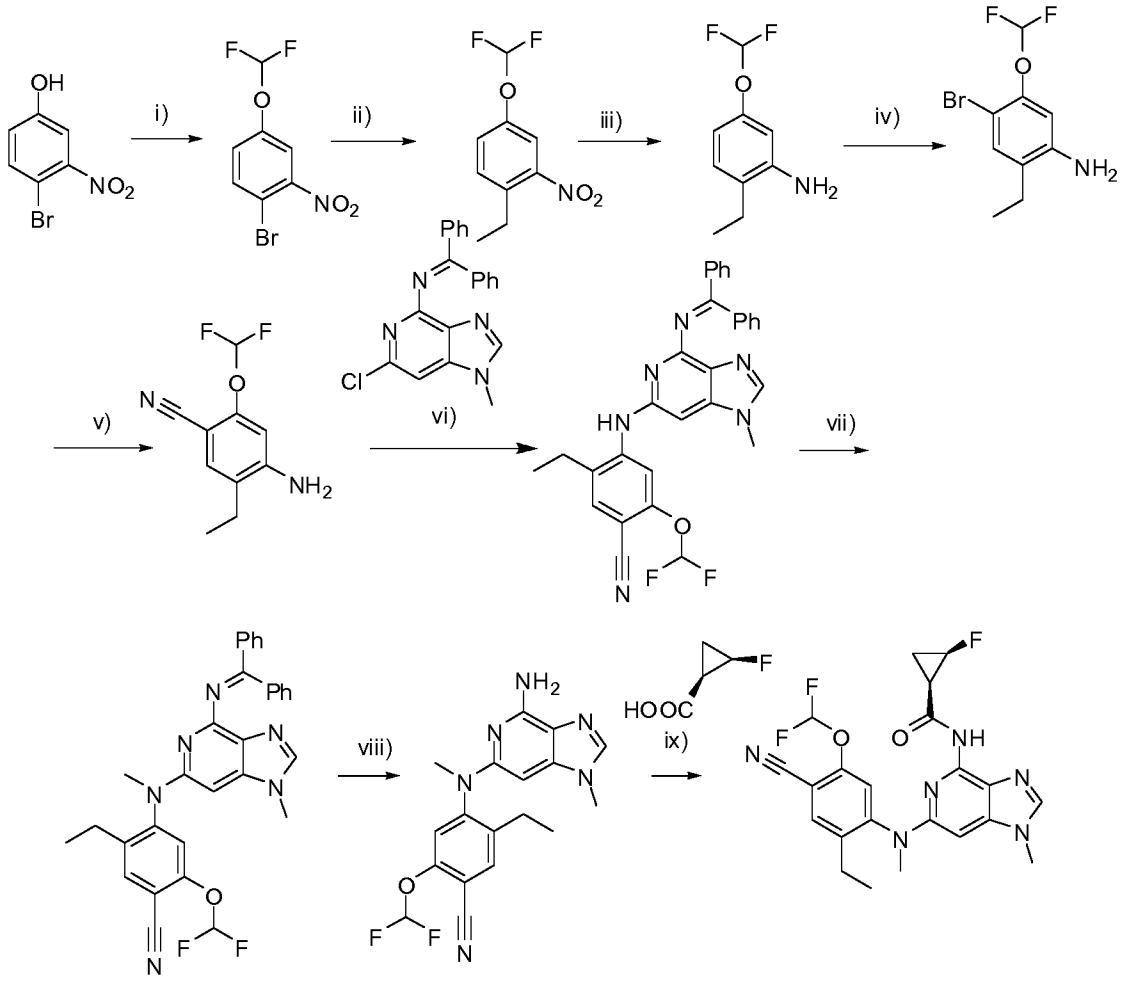
3.133.4. Step iv): 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-methyl-pyridine-2-carbonitrile

[0736] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-methyl-pyridine-2-carbonitrile as starting material.

3.133.5. Step v): (1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

[0737] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-methyl-pyridine-2-carbonitrile as starting material.

3.134. Compound 121: (1R,2R)-N-(6-((4-cyano-5-(difluoromethoxy)-2-ethylphenyl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropane carboxamide



3.134.1. Step i): 1-Bromo-4-difluoromethoxy-2-nitro-benzene

[0738] Prepared accordingly to what reported for the synthesis of intermediate 16, step i), using 4-bromo-3-nitro-phenol as starting material.

3.134.2. Step ii): 4-Difluoromethoxy-1-ethyl-2-nitro-benzene

[0739] To a suspension of cesium carbonate (66.53 mmol) and $PdCl_2(dppf)\times CH_2CL_2$ (1.11 mmol) in dry DMF (50 mL) purged with argon are added 1-Bromo-4-difluoromethoxy-2-nitro-benzene (11.09 mmol) and triethylborane, 1M solution in THF (14.4 mmol). The reaction mixture is heated in a sealed flask at 55°C. After 2 h reaction mixture is cooled down to room temperature, diluted with water (50ml) and extracted with DCM (3 x 50ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure to afford the desired product.

3.134.3. Step iii): 5-(difluoromethoxy)-2-ethyl-aniline

[0740] Prepared accordingly to what reported for the synthesis of intermediate 28, step iv), using 4-Difluoromethoxy-1-ethyl-2-nitro-benzene as starting material.

3.134.4. Step iv): 4-Bromo-5-difluoromethoxy-2-ethyl-phenylamine

[0741] 5-Difluoromethoxy-2-ethyl-phenylamine (4.77 mmol) is dissolved in PEG400 (1ml) and cooled to 0°C. Then N-bromo-succinimide (5.01) is added portionwise. After 30 min the reaction mixture is diluted with water (10ml) and extracted with DCM (3 x 10ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure. The residue is purified by flash column chromatography (SiO_2, 100:0 to 50:50 cyclohexane/EtOAc) to afford the thesired product.

3.134.5. Step v): 4-amino-2-(difluoromethoxy)-5-ethyl-benzonitrile

[0742] 4-Bromo-2-difluoromethoxy-6-fluoro-phenylamine(3.36 mmol), zinc cyanide (2.44 mmol) and Tetrakis(triphenylphosphine)palladium(0) (0.34 mmol) are dissolved in a mixture of DMF (10ml) and DMA (5 mL). After degassing, the mixture is stirred at 200°C for 2 h in a microwave reactor. The reaction mixture is diluted with water (30 mL) and extracted with DCM (3 x 30ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure. The residue is purified by flash column chromatography (SiO_2, 100:0 to 0:100 cyclohexane/EtOAc) to afford the desired product.

3.134.6. Step vi): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile

[0743] Prepared accordingly to what reported for the synthesis of compound 67, step i), using 4-amino-2-(difluoromethoxy)-5-ethyl-benzonitrile and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.134.7. Step vii): 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile

[0744] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile as starting material.

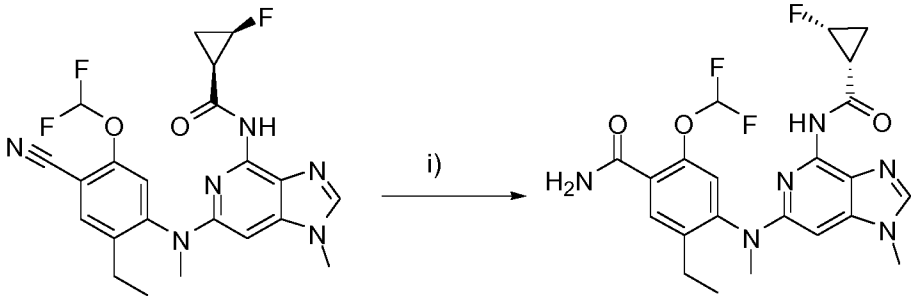
3.134.8. Step viii): 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile

[0745] 4-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile (0.51 mmol) is dissolved in dry DCM (3ml) and TFA (1.2 mL) was. The reaction mixture is stirred for 3 h. The mixture is diluted with water (10ml) and extracted with DCM (3 x 20ml). Organic layers are combined, passed through phase separator and evaporated under reduced pressure to afford the desired product.

3.134.9. Step ix): (1R,2R)-N-[6-[4-cyano-5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

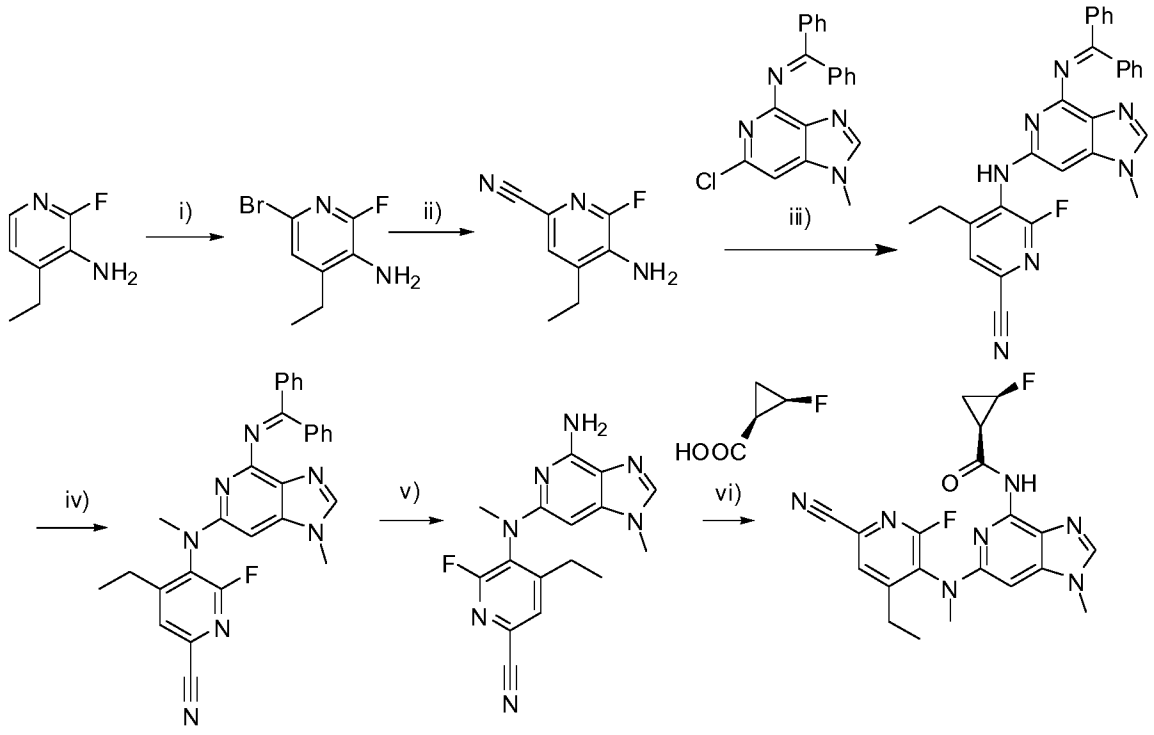
[0746] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using 4-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-2-(difluoromethoxy)-5-ethyl-benzonitrile as starting material.

3.135. Compound 122: 2-(difluoromethoxy)-5-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide



[0747] Prepared accordingly to what reported for the synthesis of compound 68, step ii), using (1R,2R)-N-[6-[4-cyano-5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide as starting material.

3.136. Compound 123:



3.136.1. Step i): 6-Bromo-4-ethyl-2-fluoro-pyridin-3-ylamine

[0748] Ethyl-2-fluoro-pyridin-3-ylamine (8.56) is dissolved in dry DCM (12ml) under nitrogen and the solution cooled with an ice bath. 1,3-Dibromo-5,5-dimethyl-imidazolidine-2,4-dione (4.28 mmol) is added in 5 portions over 40 min. After the addition is finished, the mixture is stirred at room temperature

for 2 h. The reaction is concentrated under reduced pressure and the residue is purified by flash column chromatography (SiO_2, 100:0 to 60:40 cyclohexane/EtOAc) to afford the desired product.

3.136.2. Step ii): 5-Amino-4-ethyl-6-fluoro-pyridine-2-carbonitrile

[0749] Prepared accordingly to what reported for the synthesis of Intermediate 28, step v), using 6-bromo-4-ethyl-2-fluoro-pyridin-3-ylamine as starting material.

3.136.3. Step iii): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile

[0750] Prepared accordingly to what reported for the synthesis of compound 67, step i), using 5-amino-4-ethyl-6-fluoro-pyridine-2-carbonitrile and N-(6-chloro-1-methyl-imidazo[4,5-c]pyridin-4-yl)-1,1-diphenyl-methanimine as starting materials.

3.136.4. Step iv): 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile

[0751] Prepared accordingly to what reported for the synthesis of compound 89, step ii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile as starting material.

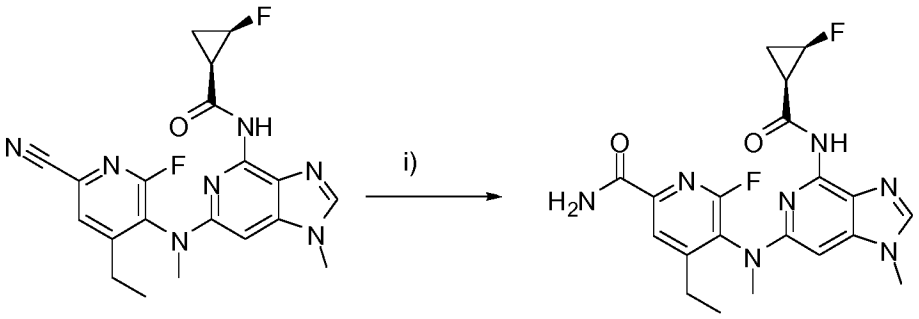
3.136.5. Step v): 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile

[0752] Prepared accordingly to what reported for the synthesis of compound 89, step iii), using 5-[[4-(benzhydrylideneamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile as starting material.

3.136.6. Step vi): (1R,2R)-N-[6-[(6-cyano-4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide

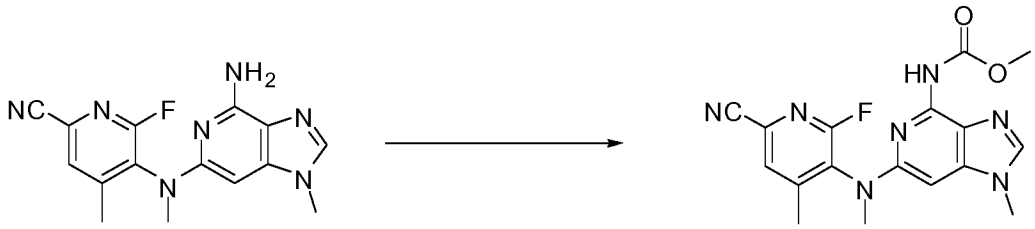
[0753] Prepared accordingly to what reported for the synthesis of compound 89, step iv), using 5-[(4-amino-1-methyl-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-ethyl-6-fluoro-pyridine-2-carbonitrile as starting material.

3.137. Compound 124: 4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-5-fluoro-benzamide



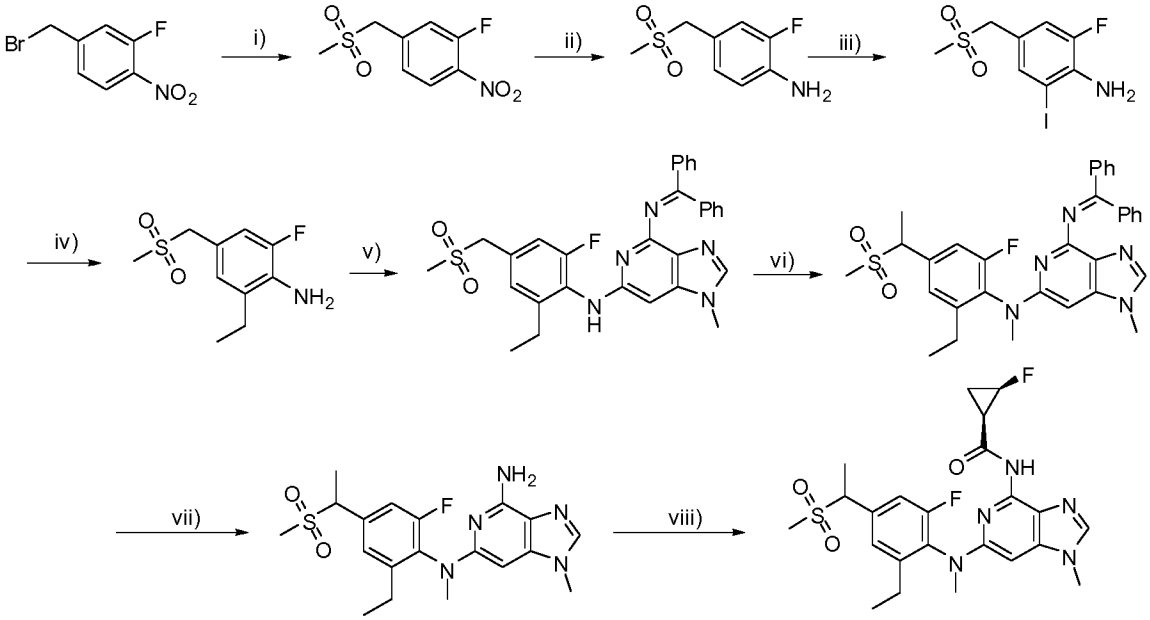
[0754] Prepared accordingly to what reported for the synthesis of compound 68, step ii), using (1R,2R)-N-[6-[(6-cyano-4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide as starting material.

3.138. Compound 125: methyl N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate



[0755] To aminopyridine (1.0 eq, 150 mg) and dry pyridine (3.0 eq, 0.12 mL) in dry DCM (4 mL) is added methyl chloroformate (3.0 eq, 0.11 mL). The reaction mixture is stirred at 50°C overnight. The resulting mixture is diluted with DCM. The organic phase is washed aq. sat. $NaHCO_3$ solution, passed through a phase separator and concentrated. The residue is purified by silica chromatography (EtOAc: NH3 in MeOH 100:0 to 50:2) to give the desired product.

3.139. Compound 126: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[2-ethyl-6-fluoro-4-(1-methanesulfonyl-ethyl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide



3.139.1. Step i : 2-Fluoro-4-methanesulfonylmethyl-1-nitro-benzene

[0756] 3-Fluoro-4-nitrobenzyl bromide (1.0 eq, 500 mg) and sodium methanesulfinate (1.5 eq, 328 mg) in DMF (2 mL) are heated at 65 °C for 1 h. The resulting mixture is diluted with EtOAc, washed with water, dried and concentrated to afford the desired product that is used as such

3.139.2. Step ii : 2-Fluoro-4-methanesulfonylmethyl-phenylamine

[0757] A mixture of the nitroaryl (1 eq), zinc powder (10 eq, 1.4 g), NH_4Cl (cat.) in formic acid (4 mL) and MeOH (20 mL) is heated at 80 °C for 45 min. The resulting mixture is filtered through Celite and concentrated. The residue is rediluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated to give the expected compound.

3.139.3. Step iii : 2-Fluoro-6-iodo-4-methanesulfonylmethyl-phenylamine

[0758] A mixture of the aniline (1 eq, 272 mg), iodine (1 eq, 340 mg), silver sulfate (1 eq, 418 mg) in EtOH (5 mL) is stirred at rt for 1.5 h. The resulting mixture is filtered and concentrated. The residue is rediluted with DCM, washed with aq. sat. $Na_2S_2O_3$, passed through a phase separator and concentrated. Used without further purification.

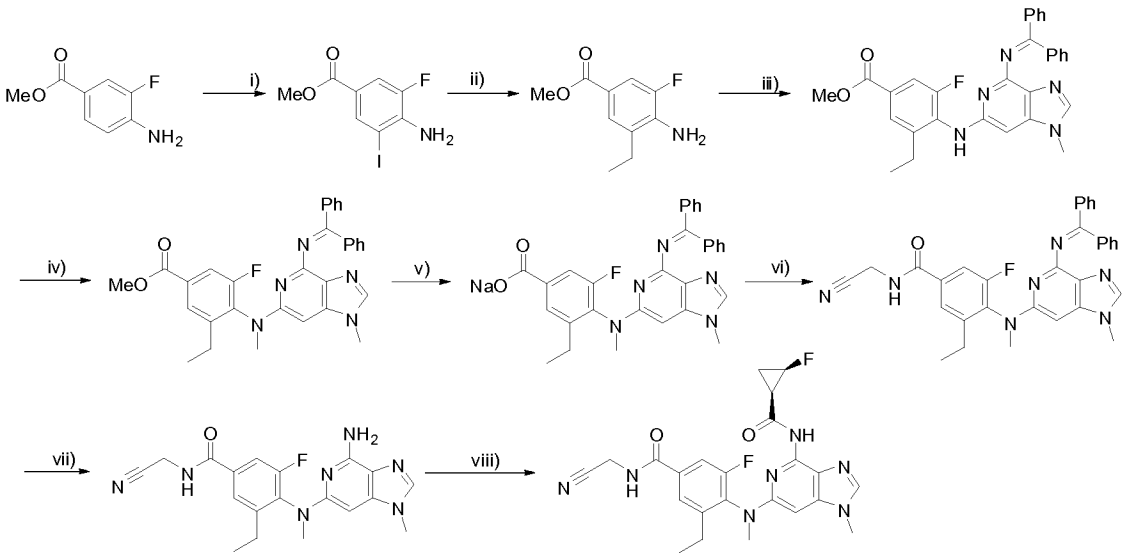
3.139.4. Step iv : 2-Ethyl-6-fluoro-4-methanesulfonylmethyl-phenylamine

[0759] A mixture of the iodo-aryl (1.0 eq), BEt_3 (1M in THF, 1.3 eq, 1.7 mL), $PdCl_2dppf$ (0.1 eq, 106 mg) and Cs_2CO_3 (3.0 eq, 1.31 g) in DMF (8 mL) is stirred at 60 °C for 1 h. The mixture is filtered on Celite and concentrated. The resulting residue is rediluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated. Purification by silica chromatography (EtOAc/petrol ether; 50:50) affords the desired compound.

3.139.5. Steps v to viii: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid (6-{[2-ethyl-6-fluoro-4-(1-methanesulfonyl-ethyl)-phenyl]-methyl-amino}-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-amide

[0760] Synthesised following the same conditions used for compound 47 (*step ii to v).*

3.140. Compound 127: N-Cyanomethyl-3-ethyl-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-benzamide



3.140.1. Step i and ii : 4-Amino-3-ethyl-5-fluoro-benzoic acid methyl ester

[0761] Synthesised following the same conditions used for compound 126 (*step iii and iv).* Purification by silica chromatography (EtOAc/petrol ether; 20:80) affords the desired compound.

3.140.2. Step iii : 4-[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-lamino]-3-ethyl-5-fluoro-benzoic acid methyl ester

[0762] Synthesised following the same conditions used for compound 47 (*step ii).*

3.140.3. Step iv : 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzoic acid methyl ester

[0763] NaH (60%, 1.0 eq, 89 mg) is added to a solution of the amine (1.0 eq, 1.13 g) in DMF (10 mL) at 0 °C. After 5 min, MeI (1.0 eq, 139 µL) is added and the solution is stirred for 1 h. The resulting mixture is diluted with DCM, washed with aq. sat. $NaHCO_3$, passed through a phase separator and concentrated.

3.140.4. Step v : 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-3-ethyl-5-fluoro-benzoic acid

[0764] A solution of the aryl-ester (1.00 eq, 0.75 g) and NaOH (1.05 eq, 60 mg) in THF (12 mL) and water (2 mL) is heated at 100 °C for 20 min in a microwave reactor after what the mixture is concentrated. The residue is used in the next step without further purification.

3.140.5. Step vi : 4-{[4-(Benzhydrylidene-amino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl]-methyl-amino}-N-cyanomethyl-3-ethyl-5-fluoro-benzamide

[0765] Amino-acetonitrile (2 eq, 44 mg) is added to a solution of the acid (1.00 eq, 200 mg), HATU (1.1 eq, 163 mg) and NEt_3 (3 eq, 163 µL) in DMF (2 mL) and the mixture is stirred at rt for 2 h. The resulting mixture is diluted with DCM, washed with water, passed through a phase separator and concentrated to afford the crude residue that is used as such in the next step.

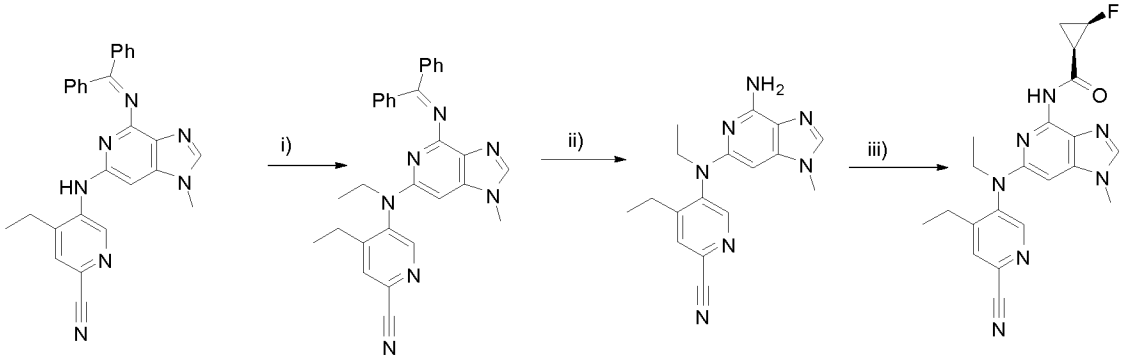
3.140.6. Step vii: N-Cyanomethyl-3-ethyl-5-fluoro-4-({4-[((1R,2R)-2-fluoro-cyclopropanecarbonyl)-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl}-methyl-amino)-benzamide

[0766] Synthesised following the same conditions used for compound 47 (*step iv*).

3.140.7. Step viii : 4-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-N-cyanomethyl-3-ethyl-5-fluoro-benzamide

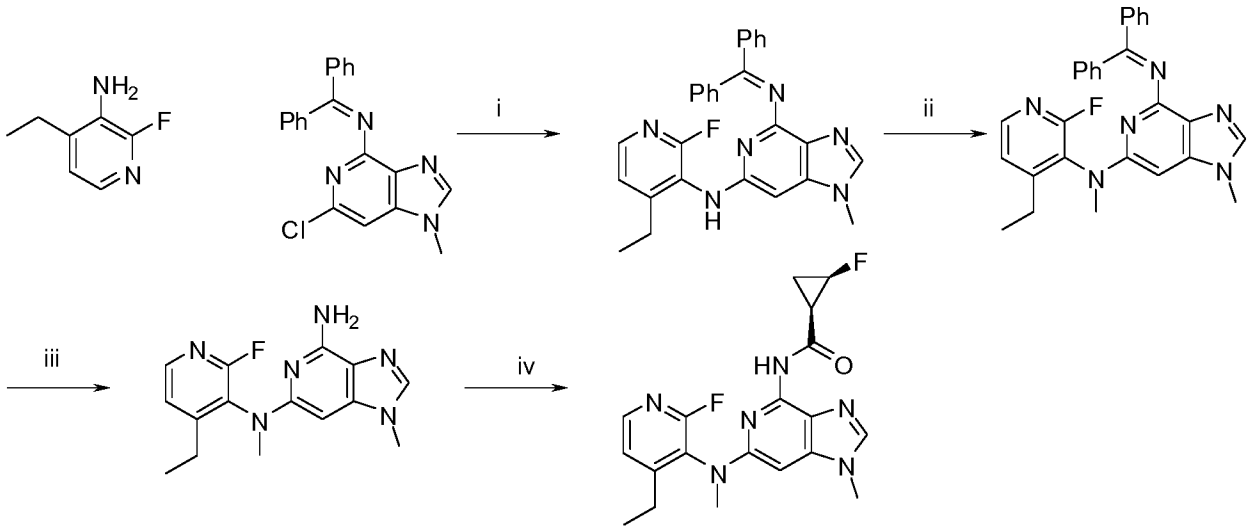
[0767] To (R,R)-2-fluoro-cyclopropanecarboxylic acid (3.5 eq, 77 mg) in dry DCM (1.5 mL) at 0 °C is added oxalyl chloride (3.5 eq, 63 µL) followed by 1 drop of DMF. After 15 min, a suspension of the amine (1 eq, 80 mg) in dry DCM (1 mL) is added, followed by pyridine (0.25 mL), and the mixture is stirred for 18 h. The crude mixture is diluted with DCM, washed with aq. sat. NH_4Cl, dried and concentrated. The mixture is purified by preparative HPLC.

3.141. Compound 128: (1R,2R)-N-(6-((6-cyano-4-ethylpyridin-3-yl)(ethyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)-2-fluorocyclopropanecarboxamide



[0768] For steps i), ii) and iii) the procedures used for compound 70 (iv, v and vi) are followed.

3.142. Compound129: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-ethyl-2-fluoro-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide



3.142.1. Step i: N4-Benzhydrylidene-N6-(4-ethyl-2-fluoro-pyridin-3-yl)-1-methyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0769] Synthesized following the same conditions used for compound 63 (step iv).

3.142.2. Step ii: N4-Benzhydrylidene-N6-(4-ethyl-2-fluoro-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0770] Synthesized following the same conditions used for compound 63 (step v).

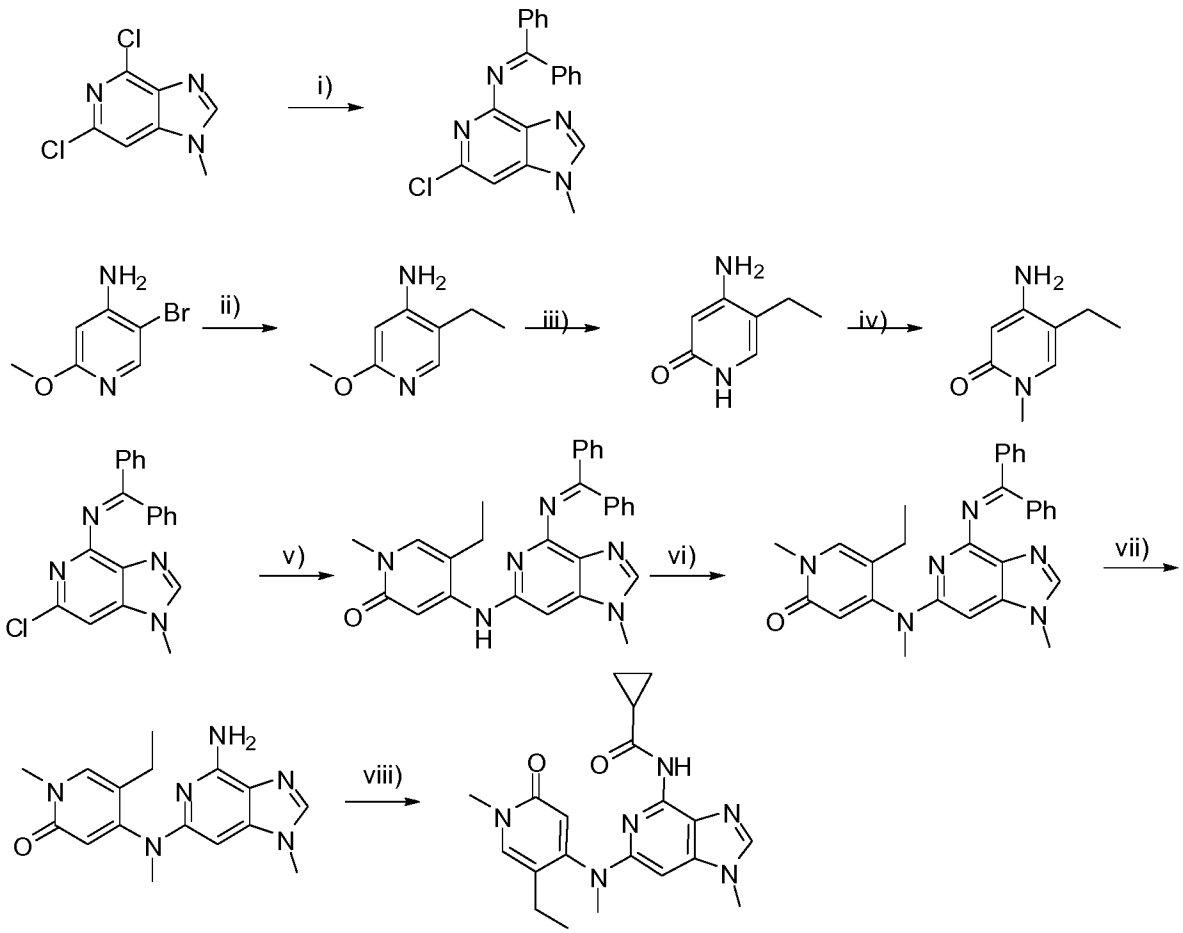
3.142.3. Step iii: N6-(4-Ethyl-2-fluoro-pyridin-3-yl)-1,N6-dimethyl-1H-imidazo[4,5-c]pyridine-4,6-diamine

[0771] Synthesized following the same conditions used for compound 63 (step vi).

3.142.4. Step iv: (1R,2R)-2-Fluoro-cyclopropanecarboxylic acid {6-[(4-ethyl-2-fluoro-pyridin-3-yl)-methyl-amino]-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl}-amide

[0772] Synthesized following the same conditions used for compound 65 (step v).

3.143. Compound 130: N-(6-((5-ethyl-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide



3.143.1. Step i: 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine

[0773] A mixture of 4,6-dichloro-1-methyl-1H-imidazo[4,5-c]pyridine (8 g, 1 eq), BINAP (1.85 g. 0.075 eq), benzophenone imine (7.2 g, 1 eq), tBuONa (4.9 g, 1.3 eq) and $Pd(OAc)_2$ (450 mg, 0.05 eq) in toluene (160 mL) is stirred at 80 °C for 3 h. The mixture is diluted (EtOAc), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated. The residue is triturated with EtOAc to yield the desired product.

3.143.2. Step ii: 5-ethyl-2-methoxypyridin-4-amine

[0774] A mixture of Cs_2CO_3 (49 g, 6 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (2 g, 0.1 eq) is suspended in DMF (100 mL). 1 M Et_3B in THF (37 mL, 1.5 eq), 5-bromo-2-methoxypyridin-4-amine (5 g, 1 eq) and H_2O are added in this order and the mixture is stirred at 80 °C for 1 hr. The mixture is concentrated, diluted (EtOAc), washed (sat. $NaHCO_3$), dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 80:20 to 50:50 petroleum ether/EtOAc) to yield the desired product.

3.143.3. Step iii: 4-amino-5-ethylpyridin-2(1H)-one

[0775] A mixture of 5-ethyl-2-methoxypyridin-4-amine (3 g) in conc. HCl (30 mL) is split in three and stirred at 105 °C for 17 h in closed vessels. The mixtures are combined and concentrated to yield the desired product.

3.143.4. Step iv: 4-amino-5-ethyl-1-methylpyridin-2(1H)-one

[0776] MeI (224 µL, 3.6 eq) is added to a mixture of 4-amino-5-ethylpyridin-2(1H)-one (700 mg) and 60% mineral oil NaH (352 mg, 2.2 eq) in DMF (10 mL). The mixture is stirred at room temperature for 15 h. The mixture is diluted (DCM), quenched (H_2O, sat. $NaHCO_3$) and the two layers are separated. The aqueous layer is saturated with NaCl and extracted (THF). The THF solution is concentrated and the residue purified by flash column chromatography (SiO_2, 100:0 to 95:5 DCM/MeOH) to yield the desired product.

3.143.5. Step v: 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethyl-1-methylpyridin-2(1H)-one

[0777] Two mixtures of the 4-amino-5-ethyl-1-methylpyridin-2(1H)-one (1 eq, 75 mg), 6-chloro-N-(diphenylmethylene)-1-methyl-1H-imidazo[4,5-c]pyridin-4-amine (1.0 eq, 174 g), $Pd(OAc)_2$ (0.2 eq, 23 mg), BINAP (0.3 eq, 94 mg) and Cs_2CO_3 (4.5 eq, 733 mg) in dry dioxane (2.5 mL) in two different sealed tubes are stirred at 110 °C for 1 h. Additional 0.1 mmol of catalyst, 0.15 mmol of ligand and 0.5 mL of solvent are added to each mixture. The mixtures are stirred for 16 h at110 °C. The mixtures are combined, diluted (DCM), washed (sat. $NaHCO_3$) and dried (filtered through phase separator) to yield the desired product.

3.143.6. Step vi: 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-1-methylpyridin-2(1H)-one

[0778] NaH (100 mg, 2.5 eq) is added to a mixture of 4-(4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-ylamino)-5-ethyl-1-methylpyridin-2(1H)-one (1 mmol) in THF (20 mL). The mixture is stirred for 30 min at 0 °C. MeI (154 µL, 2.5 eq) is added to the mixture. The reaction is stirred at 0 ° for 1 hr. The mixture is diluted (DCM), quenched (H_2O, sat. $NaHCO_3$), dried (filtered through phase separator) and concentrated to yield the desired product.

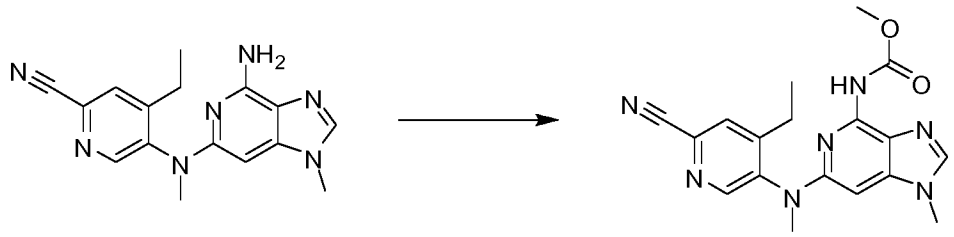
3.143.7. Step vii: 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-1-methylpyridin-2(1H)-one

[0779] A mixture of 4-((4-(diphenylmethyleneamino)-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-1-methylpyridin-2(1H)-one (1 mmol) in 1:1 THF/2M HCl is stirred at room temperature for 1 hr. EtOAc is added and the two layers are separated. The aqueous solution is concentrated to yield the desired product.

3.143.8. Step viii: N-(6-((5-ethyl-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)(methyl)amino)-1-methyl-1H-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide

[0780] Cyclopropanecarbonyl chloride (209 mg, 2eq) is added to a mixture of 4-((4-amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)(methyl)amino)-5-ethyl-1-methylpyridin-2(1H)-one (1 mmol) and pyridine (400 µL, 5 eq) in DCM (5 mL) at 0 °. The mixture is stirred while let to reach slowly room temperature for 1 hr. The mixture is diluted (DCM), washed (sat. $NaHCO_3$), dried (filtered through phase separator) and concentrated. The residue is submitted to prep. HPLC purification to yield the desired product.

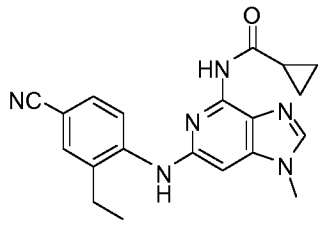
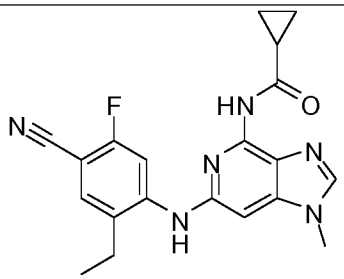
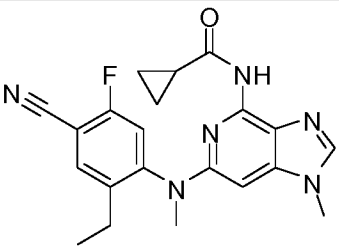
3.144. Compound 131: methyl N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate

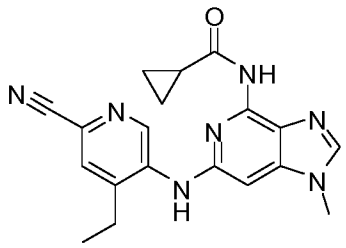
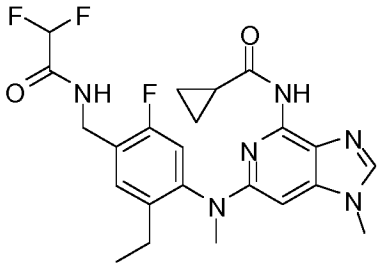
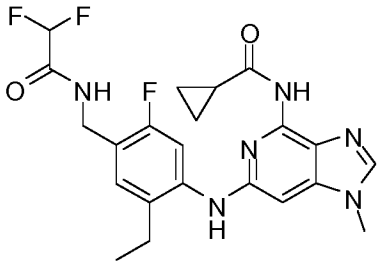
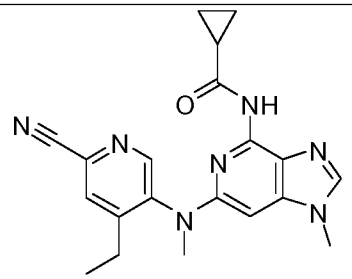
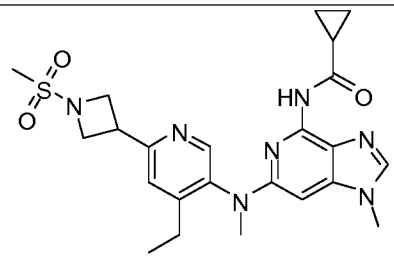
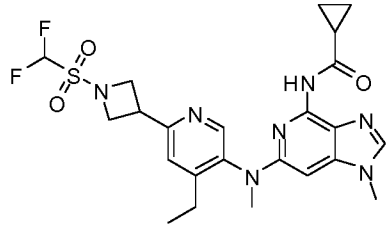


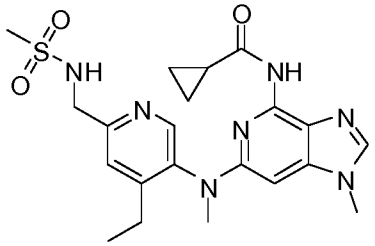
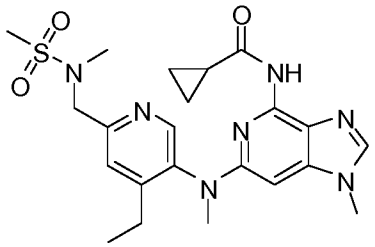
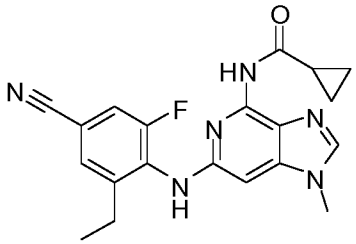
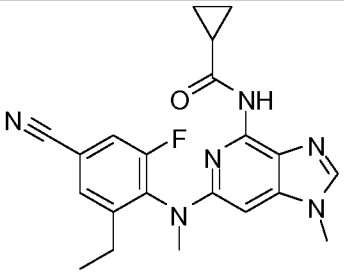
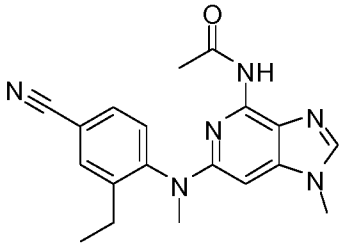
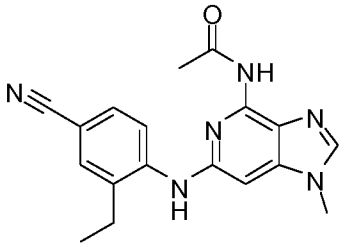
[0781] A solution of 5-[(4-Amino-1-methyl-1H-imidazo[4,5-c]pyridin-6-yl)-methyl-amino]-4-ethyl-pyridine-2-carbonitrile (0.65 mmol) in N-methyl pyrrolidone (4 mL) is added dropwise to a solution of MeOCOCl (1.3 mmol) in DCM (10 mL) at 0 °C. The mixture is stirred at room temperature for 1 h. A further 10 equivalents of MeOCOCl are added and the mixture is stirred at room temperature for 24 h. The mixture is diluted (DCM), washed (sat. $NaHCO_3$), dried (filtered through phase separator) and concentrated. The residue is taken up in EtOAc and the organic solution is washed (3 x H_2O). The mixture is dried (Na_2SO_4) and concentrated. The residue is purified by flash column chromatography (SiO_2, 100:0 to 70:30 DCM/THF). The solid so obtained is triturated with Et_2O to afford the desired product.

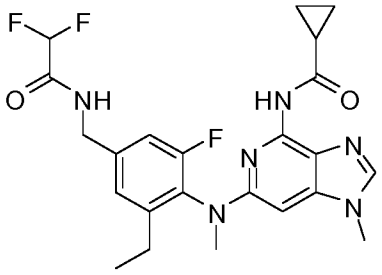
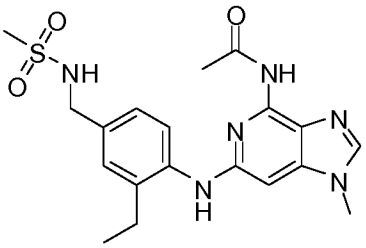
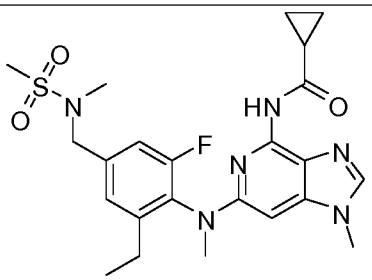
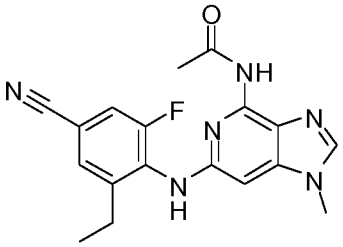
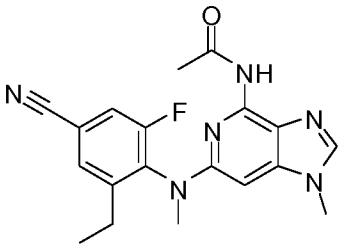
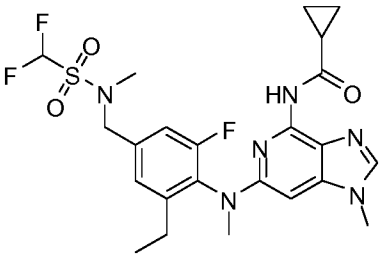
[0782] The illustrative compounds of the invention that have been prepared according to the synthetic methods described herein are listed below. The NMR spectral data of the compounds of the invention are also given below.

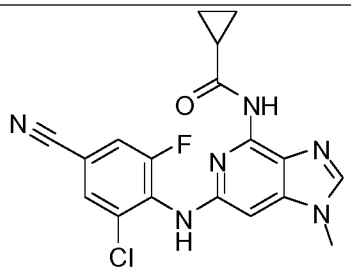
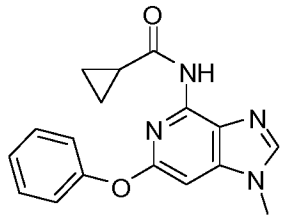
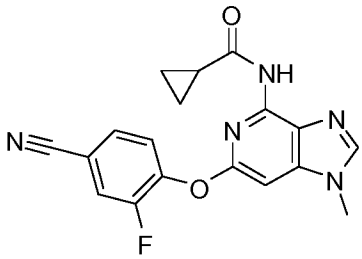
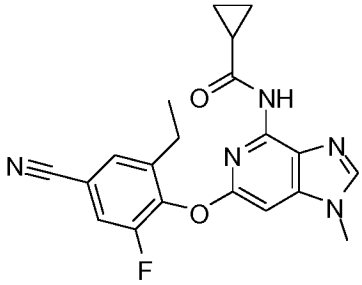
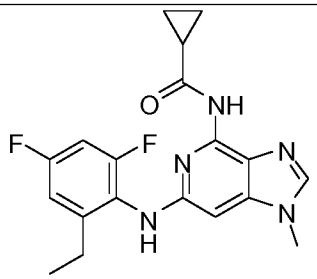
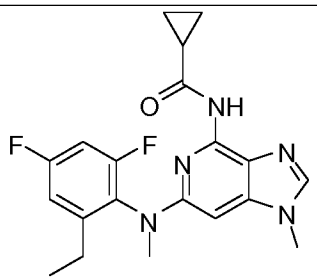
Table II. Illustrative Compound of the invention

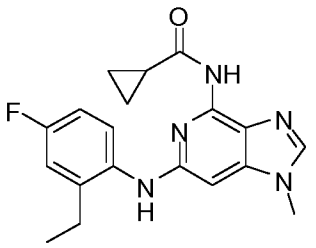
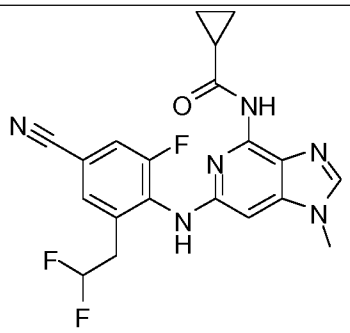
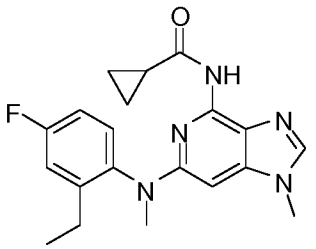
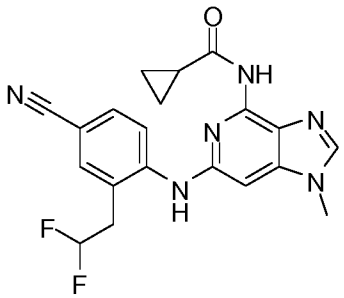
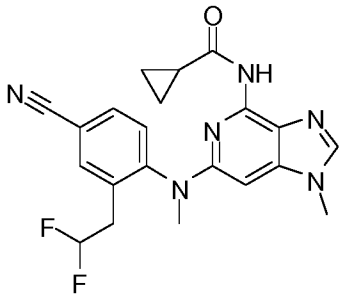
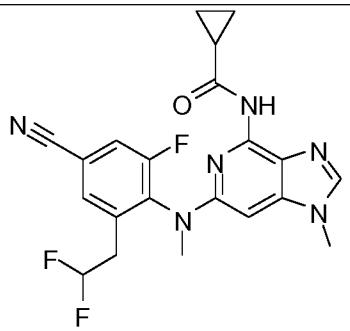
Cpd #	Structure	Name	MW	MS Ms'd
1		N-[6-(4-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	360	361
2		N-[6-(4-cyano-2-ethyl-5-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	378	379
3		N-[6-(4-cyano-2-ethyl-5-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	392	393

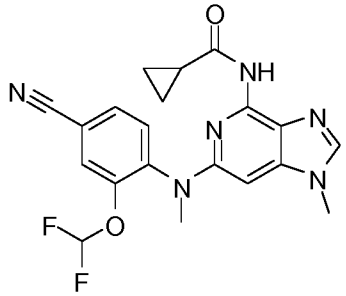
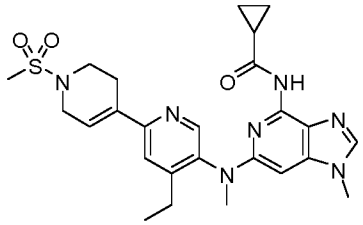
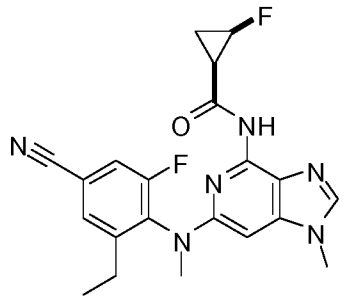
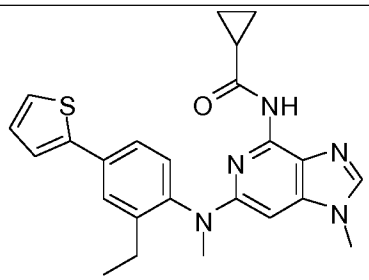
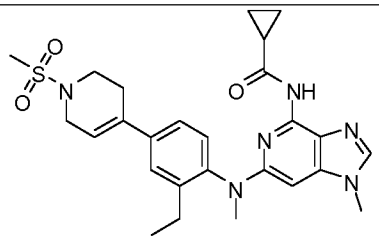
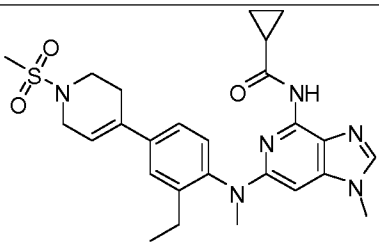
Cpd #	Structure	Name	MW	MS Ms'd
4		N-[6-[(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	361	362
5		N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-5-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	474	475
6		N-[6-[4-[[(2,2-difluoro acetyl)amino]methyl]-2-ethyl-5-fluoro-anilino]-1-methyl-imidazo[4,5-c] pyridin-4-yl] cyclopropanecarboxamide	460	461
7		N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide	375	376
8		N-[6-[[4-ethyl-6-(1-methylsulfonylazetidin-3-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	484	484
9		N-[6-[[6-[1-(difluoromethylsulfonyl)azetidin-3-yl]-4-ethyl-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide	520	520

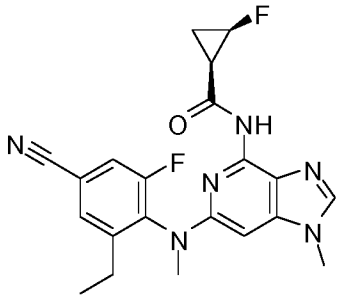
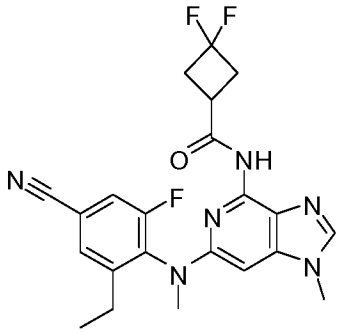
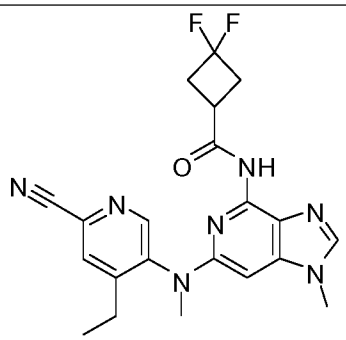
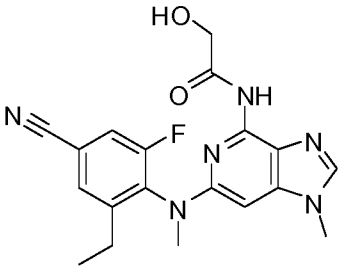
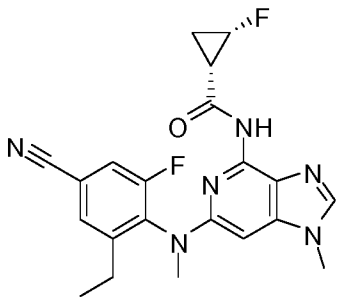
Cpd #	Structure	Name	MW	MS Ms'd
10		N-[6-[[4-ethyl-6-(methanesulfonamido methyl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	458	458
11		N-[6-[[4-ethyl-6-[[methyl(methylsulfonyl)amino]methyl]-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	472	472
12		N-[6-(4-cyano-2-ethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	378	379
13		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl] cyclopropanecarboxamide	392	393
14		N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	348	349
15		N-[6-(4-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	334	335

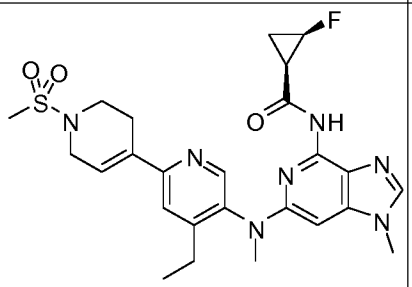
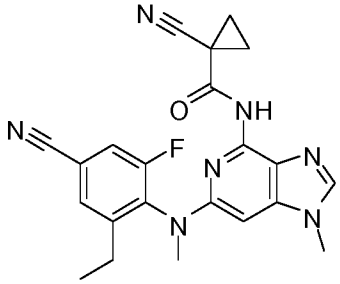
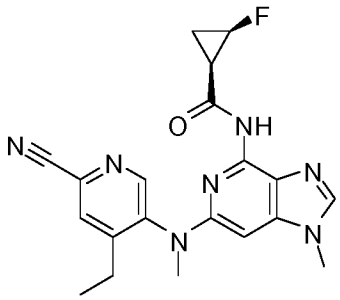
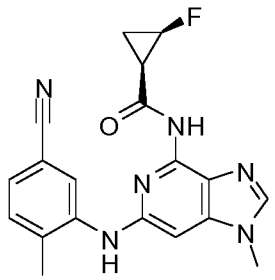
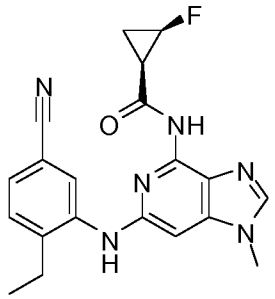
Cpd #	Structure	Name	MW	MS Ms'd
16		N-[6-[4-[[(2,2-difluoroacetyl)amino]methyl]-2-ethyl-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	474	475
17		N-[6-[2-ethyl-4-(methanesulfonamidomethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	417	417
18		N-[6-[2-ethyl-6-fluoro-N-methyl-4-[[methyl(methylsulfonyl)amino]methyl]anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	489	489
19		N-[6-(4-cyano-2-ethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	352	353
20		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	366	367
21		N-[6-[4-[[difluoromethylsulfonyl(methyl)amino]methyl]-2-ethyl-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	525	525

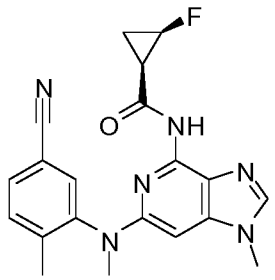
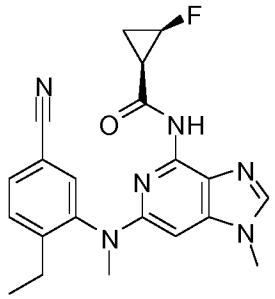
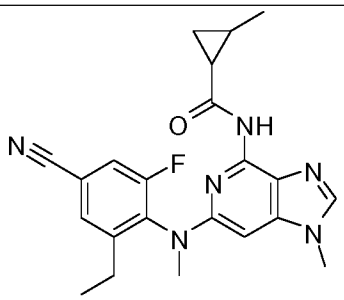
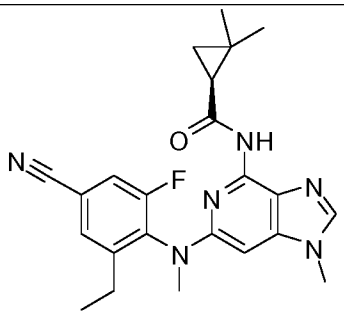
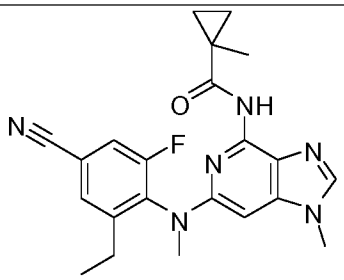
Cpd #	Structure	Name	MW	MS Ms'd
22		N-[6-(2-chloro-4-cyano-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	385	385
23		N-(1-methyl-6-phenoxy-imidazo[4,5-c]pyridin-4-yl)cyclopropanecarboxamide	308	309
24		N-[6-(4-cyano-2-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	351	352
25		N-[6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	379	366
26		N-[6-(2-ethyl-4,6-difluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	371	372
27		N-[6-(2-ethyl-4,6-difluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	385	386

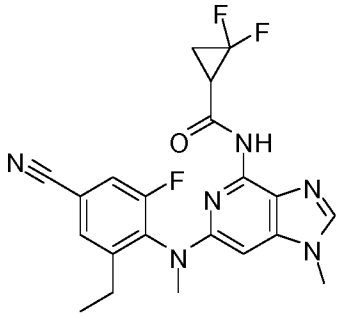
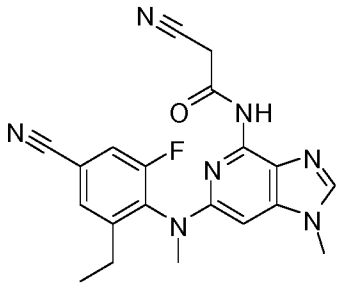
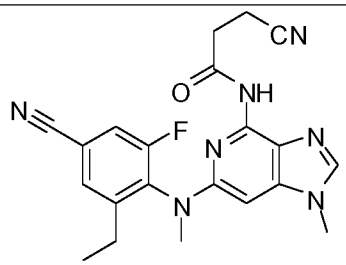
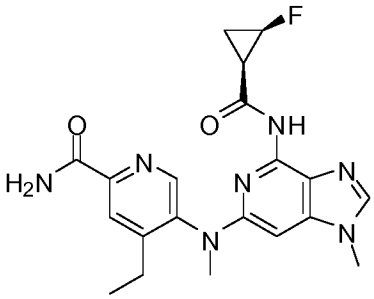
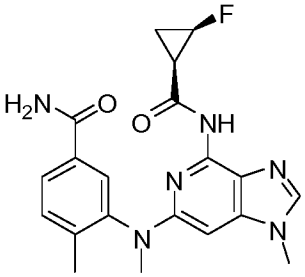
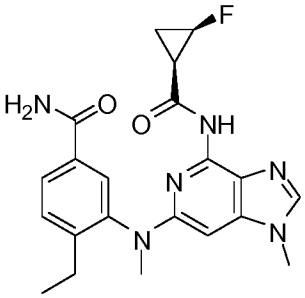
Cpd #	Structure	Name	MW	MS Ms'd
28		N-[6-(2-ethyl-4-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	353	354
29		N-[6-[4-cyano-2-(2,2-difluoroethyl)-6-fluoro-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	414	415
30		N-[6-(2-ethyl-4-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	367	368
31		N-[6-[4-cyano-2-(2,2-difluoroethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	396	397
32		N-[6-[4-cyano-2-(2,2-difluoroethyl)-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	410	411
33		N-[6-[4-cyano-2-(2,2-difluoroethyl)-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	428	429

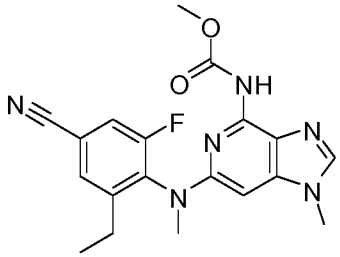
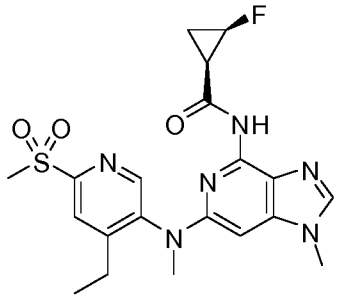
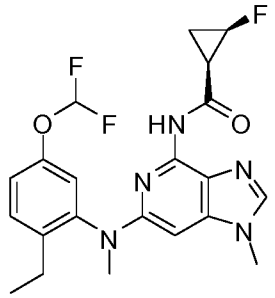
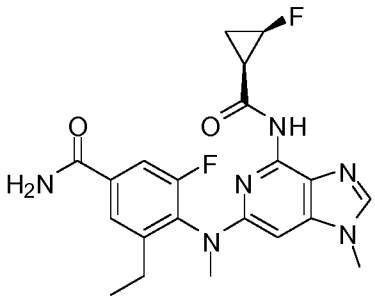
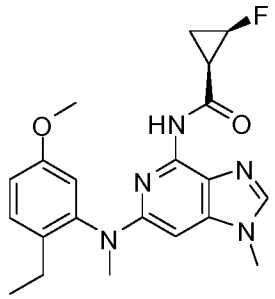
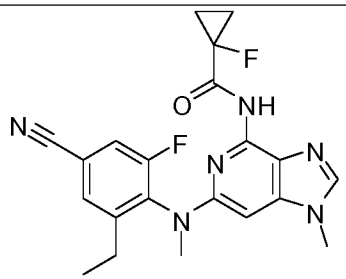
Cpd #	Structure	Name	MW	MS Ms'd
34		N-[6-[4-cyano-2-(difluoromethoxy)-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	412	413
35		N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	510	510
36		(2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	410	411
37		N-[6-[2-ethyl-N-methyl-4-(2-thienyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	432	432
38		N-[6-[2-ethyl-N-methyl-4-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	509	509
39		(1R,2R)-N-[6-[2-ethyl-N-methyl-4-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	527	527

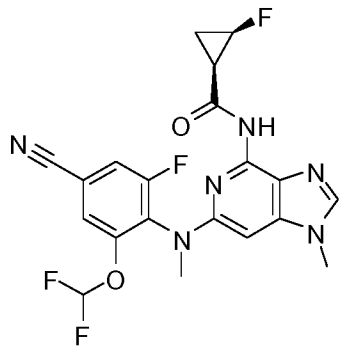
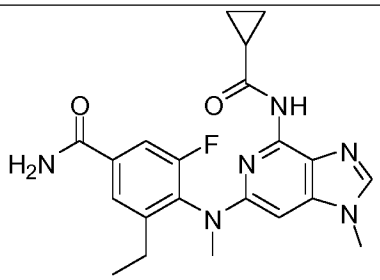
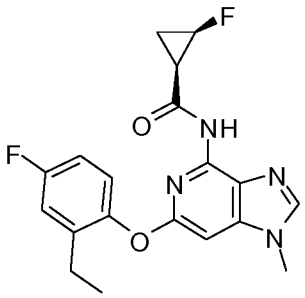
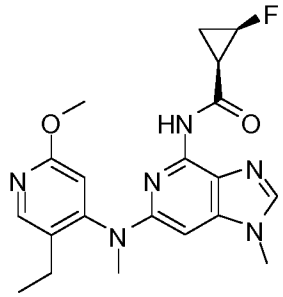
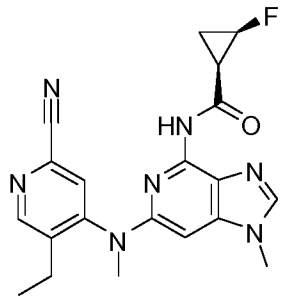
Cpd #	Structure	Name	MW	MS Ms'd
40		(1R,2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	410	411
41		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-3,3-difluoro-cyclobutanecarboxamide	442	443
42		N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-3,3-difluoro-cyclobutanecarboxamide	425	426
43		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-hydroxy-acetamide	382	383
44		(1S,2S)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	410	411

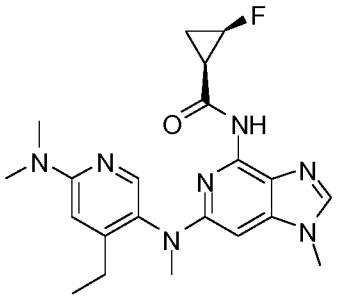
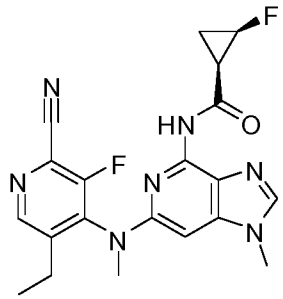
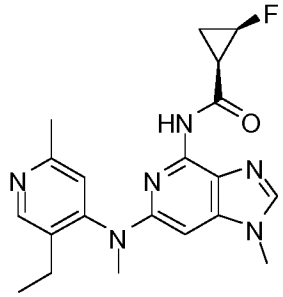
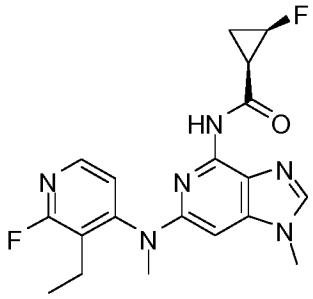
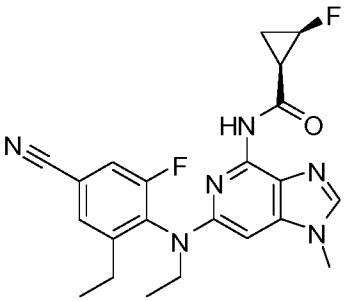
Cpd #	Structure	Name	MW	MS Ms'd
45		(1R,2R)-N-[6-[[4-ethyl-6-(1-methylsulfonyl-3,6-dihydro-2H-pyridin-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	528	528
46		1-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	417	418
47		(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	393	394
48		(1R,2R)-N-[6-(5-cyano-2-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	364	365
49		(1R,2R)-N-[6-(5-cyano-2-ethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	378	379

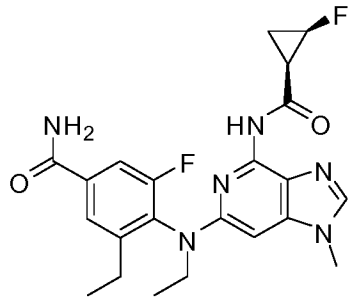
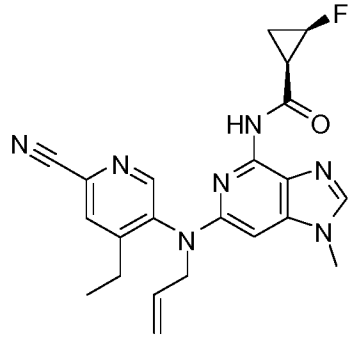
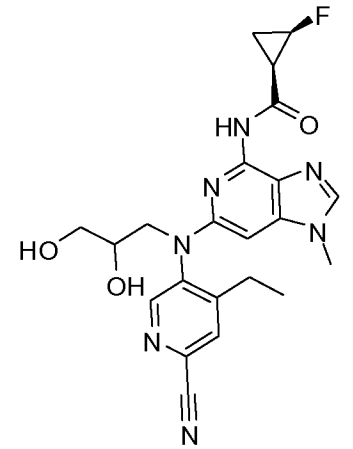
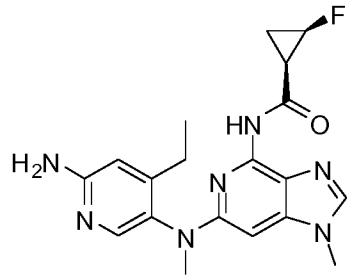
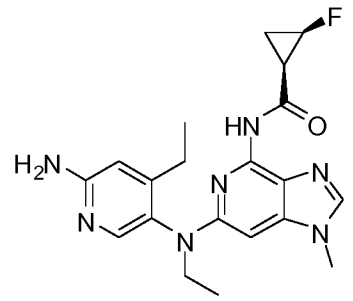
Cpd #	Structure	Name	MW	MS Ms'd
50		(1R,2R)-N-[6-(5-cyano-N,2-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	378	379
51		(1R,2R)-N-[6-(5-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	392	393
52		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-methyl-cyclopropanecarboxamide	406	407
53		(1S)-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2,2-dimethyl-cyclopropanecarboxamide	420	421
54		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-1-methyl-cyclopropanecarboxamide	406	407

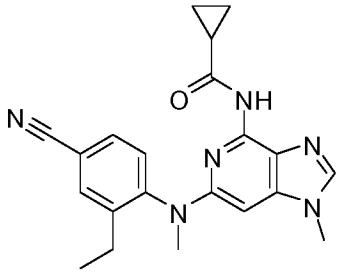
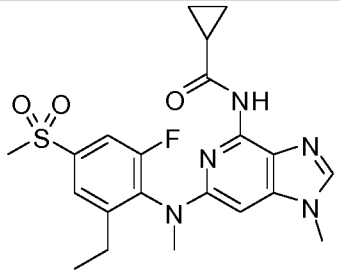
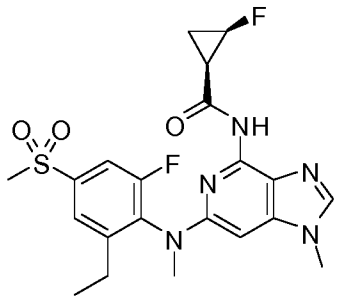
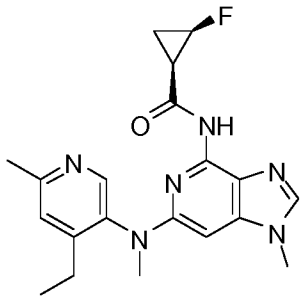
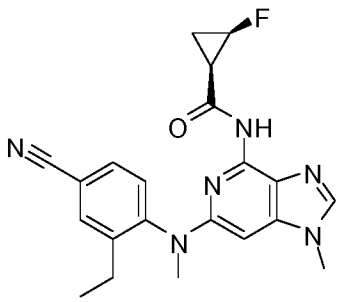
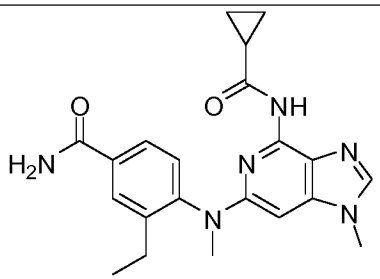
Cpd #	Structure	Name	MW	MS Ms'd
55		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2,2-difluoro-cyclopropanecarboxamide	428	429
56		2-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]acetamide	391	392
57		3-cyano-N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]propanamide	405	406
58		4-ethyl-5-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]pyridine-2-carboxamide	411	412
59		3-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-4-methyl-benzamide	396	397
60		4-ethyl-3-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	410	411

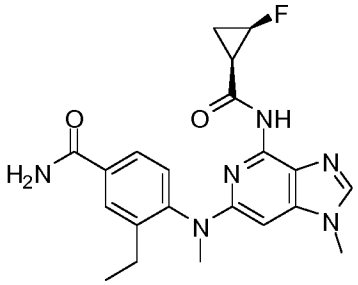
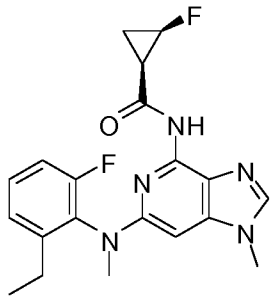
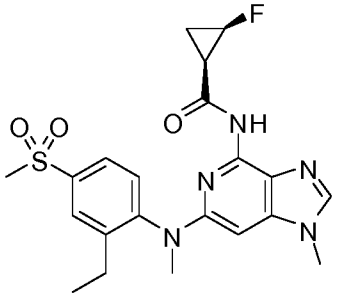
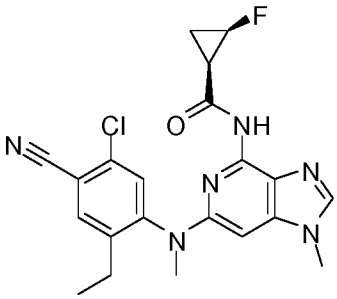
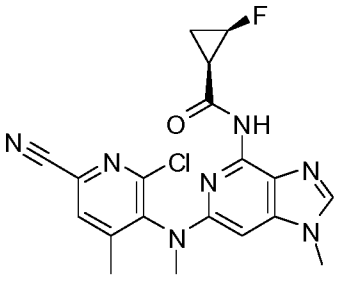
Cpd #	Structure	Name	MW	MS Ms'd
61		methyl N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate	382	383
62		(1R,2R)-N-[6-[(4-ethyl-6-methylsulfonyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	447	447
63		(1R,2R)-N-[6-[5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	433	434
64		3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	428	429
65		(1R,2R)-N-[6-(2-ethyl-5-methoxy-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	397	398
66		N-[6-(4-cyano-2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-1-fluoro-cyclopropanecarboxamide	410	411

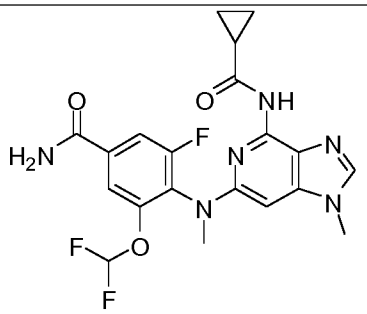
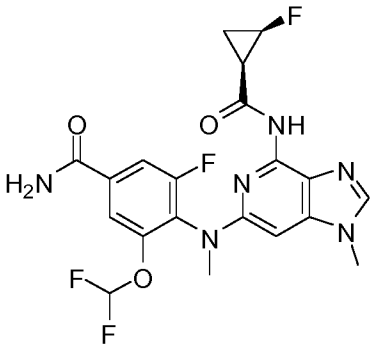
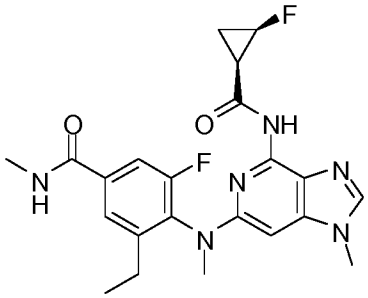
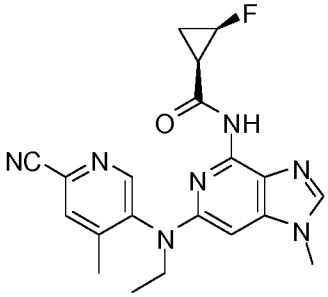
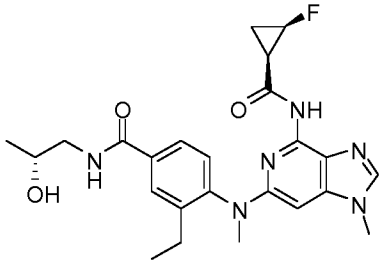
Cpd #	Structure	Name	MW	MS Ms'd
67		(1R,2R)-N-[6-[4-cyano-2-(difluoromethoxy)-6-fluoro-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	448	449
68		4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-5-fluoro-benzamide	410	411
69		(1R,2R)-N-[6-(2-ethyl-4-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	372	373
70		(1R,2R)-N-[6-[(5-ethyl-2-methoxy-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	398	400
71		(1R,2R)-N-[6-[(2-cyano-5-ethyl-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	393	395

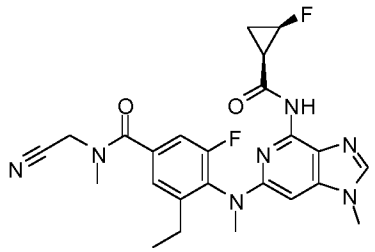
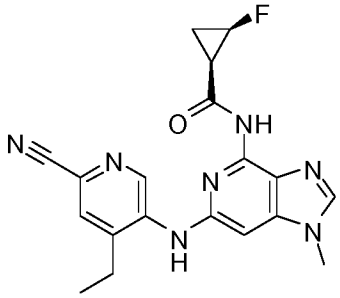
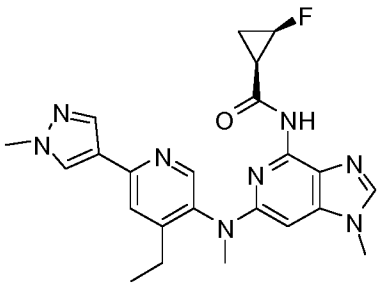
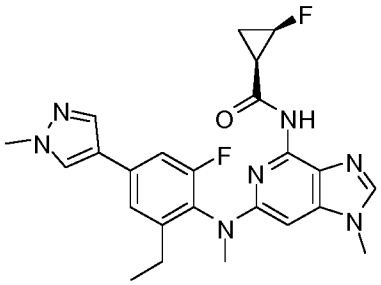
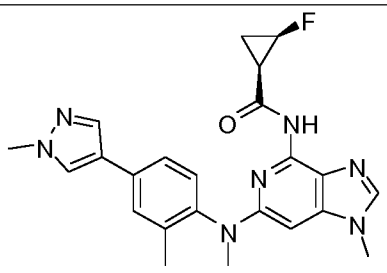
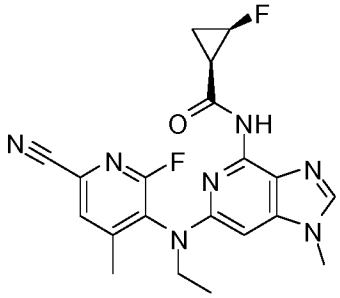
Cpd #	Structure	Name	MW	MS Ms'd
72		(1R,2R)-N-[6-[[6-(dimethylamino)-4-ethyl-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	411	413
73		(1R,2R)-N-[6-[(2-cyano-5-ethyl-3-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	411	413
74		(1R,2R)-N-[6-[(5-ethyl-2-methyl-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	382	383
75		(1R,2R)-N-[6-[(3-ethyl-2-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	386	387
76		(1R,2R)-N-[6-(4-cyano-N,2-diethyl-6-fluoro-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	424	425

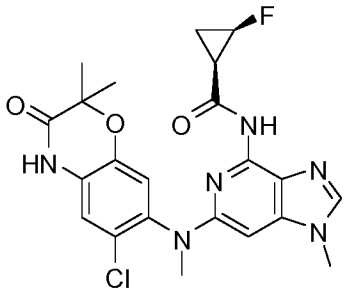
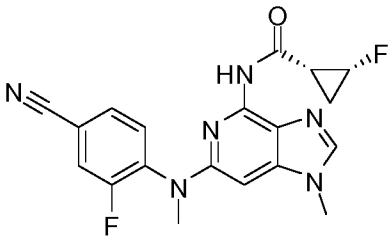
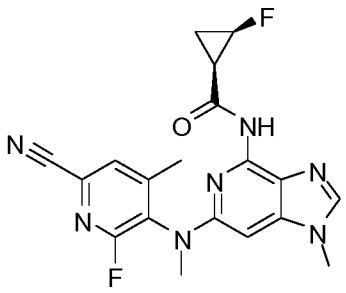
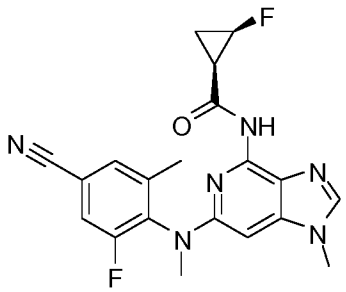
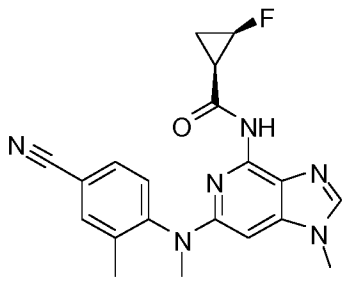
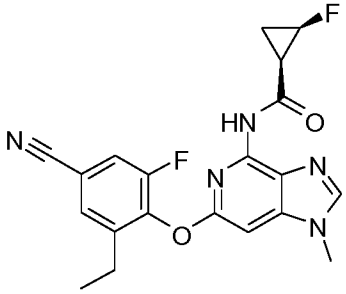
Cpd #	Structure	Name	MW	MS Ms'd
77		3-ethyl-4-[ethyl-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]amino]-5-fluoro-benzamide	442	443
78		(1R,2R)-N-[6-[allyl-(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	419	420
79		(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-(2,3-dihydroxypropyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	453	454
80		(1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	383	384
81		(1R,2R)-N-[6-[(6-amino-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	397	398

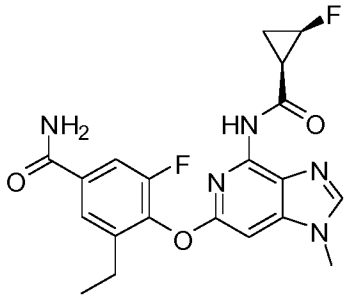
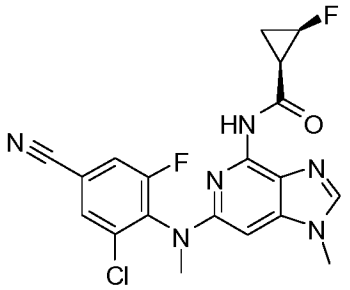
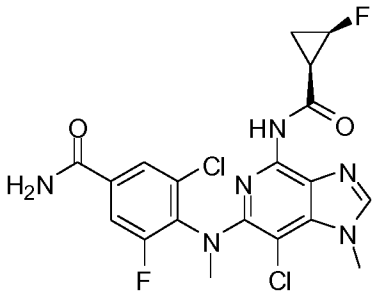
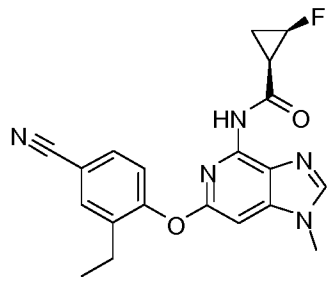
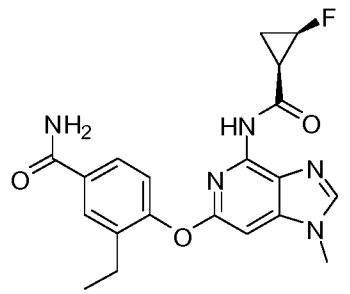
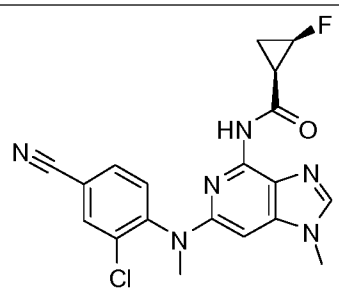
Cpd #	Structure	Name	MW	MS Ms'd
82		N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	374	375
83		N-[6-(2-ethyl-6-fluoro-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	446	446
84		(1R,2R)-N-[6-(2-ethyl-6-fluoro-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	464	464
85		(1R,2R)-N-[6-[(4-ethyl-6-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	382	383
86		(1R,2R)-N-[6-(4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	392	393
87		4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-ethyl-benzamide	392	393

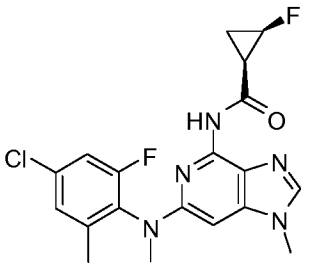
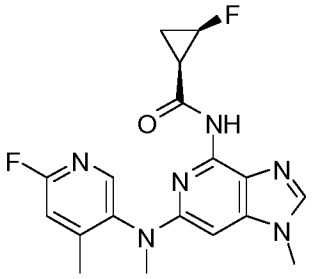
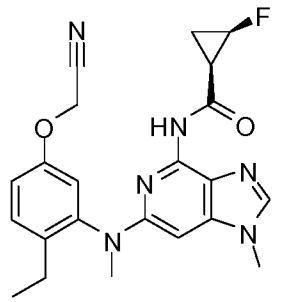
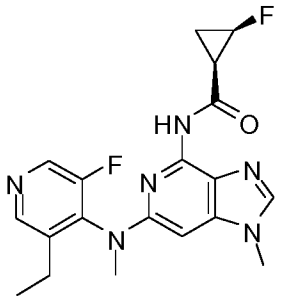
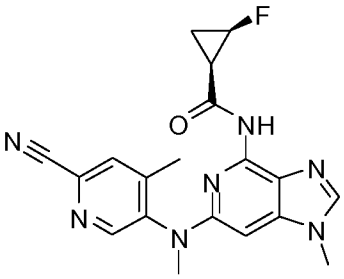
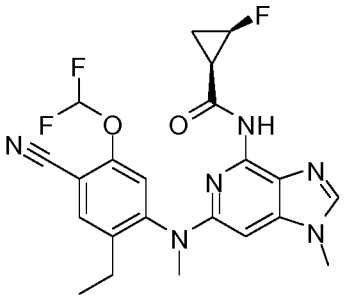
Cpd #	Structure	Name	MW	MS Ms'd
88		3-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	410	411
89		(1R,2R)-N-[6-(2-ethyl-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	385	386
90		(1R,2R)-N-[6-(2-ethyl-N-methyl-4-methylsulfonyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	446	446
91		(1R,2R)-N-[6-(5-chloro-4-cyano-2-ethyl-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	427	427
92		(1R,2R)-N-[6-[(2-chloro-6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	414	414

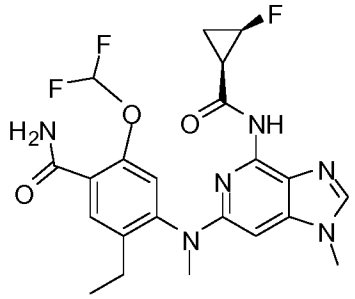
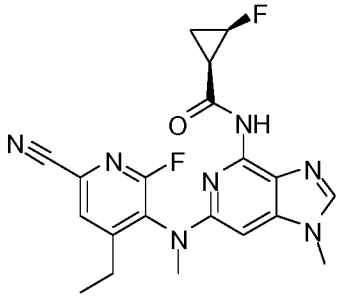
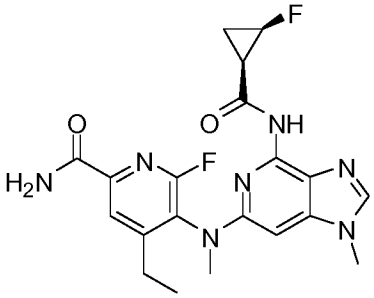
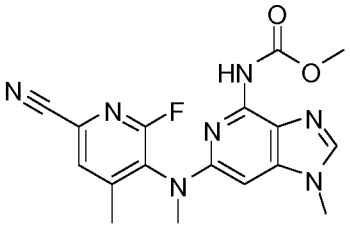
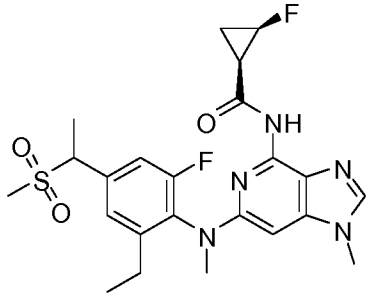
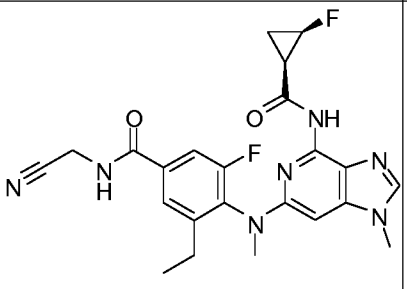
Cpd #	Structure	Name	MW	MS Ms'd
93		4-[[4-(cyclopropanecarbonylamino)-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-3-(difluoromethoxy)-5-fluoro-benzamide	448	449
94		3-(difluoromethoxy)-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	466	467
95		3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-methyl-benzamide	442	443
96		(1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	393	394
97		3-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-[(2R)-2-hydroxypropyl]benzamide	469	469

Cpd #	Structure	Name	MW	MS Ms'd
98		N-(cyanomethyl)-3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-N-methyl-benzamide	482	482
99		(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	379	380
100		(1R,2R)-N-[6-[[4-ethyl-6-(1-methylpyrazol-4-yl)-3-pyridyl]-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	449	449
101		(1R,2R)-N-[6-[2-ethyl-6-fluoro-N-methyl-4-(1-methylpyrazol-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	466	466
102		(1R,2R)-N-[6-[N,2-dimethyl-4-(1-methylpyrazol-4-yl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	433	434
103		(1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	411	412

Cpd #	Structure	Name	MW	MS Ms'd
104		(1R,2R)-N-[6-[(6-chloro-2,2-dimethyl-3-oxo-4H-1,4-benzoxazin-7-yl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	473	473
105		(1R,2R)-N-[6-(4-cyano-2-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	382	383
106		(1R,2R)-N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	397	398
107		(1R,2R)-N-[6-(4-cyano-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	396	397
108		(1R,2R)-N-[6-(4-cyano-N,2-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	378	379
109		(1R,2R)-N-[6-(4-cyano-2-ethyl-6-fluoro-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	397	398

Cpd #	Structure	Name	MW	MS Ms'd
110		3-ethyl-5-fluoro-4-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-benzamide	415	416
111		(1R,2R)-N-[6-(2-chloro-4-cyano-6-fluoro-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	417	417
112		3-chloro-4-[[7-chloro-4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]-5-fluoro-benzamide	469	469
113		(1R,2R)-N-[6-(4-cyano-2-ethyl-phenoxy)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	379	380
114		3-ethyl-4-[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]oxy-benzamide	397	398
115		(1R,2R)-N-[6-(2-chloro-4-cyano-N-methyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	399	399

Cpd #	Structure	Name	MW	MS Ms'd
116		(1R,2R)-N-[6-(4-chloro-2-fluoro-N,6-dimethyl-anilino)-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	406	406
117		(1R,2R)-2-fluoro-N-[6-[(6-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	372	373
118		(1R,2R)-N-[6-[5-(cyanomethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	422	423
119		(1R,2R)-N-[6-[(3-ethyl-5-fluoro-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	386	387
120		(1R,2R)-N-[6-[(6-cyano-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	379	380
121		(1R,2R)-N-[6-[4-cyano-5-(difluoromethoxy)-2-ethyl-N-methyl-anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	458	459

Cpd #	Structure	Name	MW	MS Ms'd
122		2-(difluoromethoxy)-5-ethyl-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	476	477
123		(1R,2R)-N-[6-[(6-cyano-4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	411	412
124		N-(6-(4-cyano-2-fluorophenoxy)-1-methyl-1H-imidazo[4,5-c] pyridin-4-yl) cyclopropane carboxamide	429	430
125		methyl N-[6-[(6-cyano-2-fluoro-4-methyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate	369	370
126		(1R,2R)-N-[6-[2-ethyl-6-fluoro-N-methyl-4-(1-methylsulfonylethyl)anilino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	492	492
127		N-(cyanomethyl)-3-ethyl-5-fluoro-4-[[4-[[(1R,2R)-2-fluorocyclopropanecarbonyl]amino]-1-methyl-imidazo[4,5-c]pyridin-6-yl]-methyl-amino]benzamide	467	468

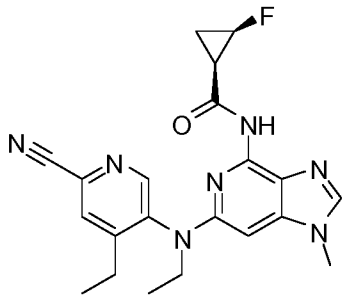
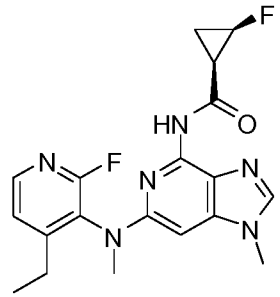
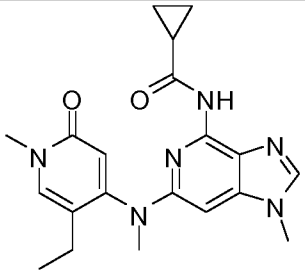
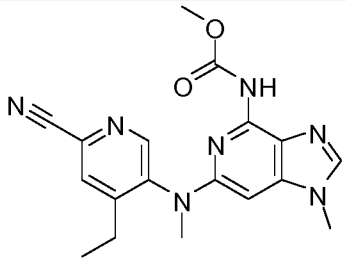
Cpd #	Structure	Name	MW	MS Ms'd
128		(1R,2R)-N-[6-[(6-cyano-4-ethyl-3-pyridyl)-ethyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	407	408
129		(1R,2R)-N-[6-[(4-ethyl-2-fluoro-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]-2-fluoro-cyclopropanecarboxamide	386	387
130		N-[6-[(5-ethyl-1-methyl-2-oxo-4-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]cyclopropanecarboxamide	380	381
131		methyl N-[6-[(6-cyano-4-ethyl-3-pyridyl)-methyl-amino]-1-methyl-imidazo[4,5-c]pyridin-4-yl]carbamate	365	366

Table III. NMR data of illustrative compounds of the invention

Cpd#	NMR spectrum
2	^{1}H NMR (300 MHz, DMSO-d_6) 10.55 (s, 1H), 8.77 (d, 1H), 8.41 (s, 1H), 8.16 (s, 1H), 7.48 (d, 1H), 7.17 (s, 1H), 3.77 (s, 3H), 2.72 (q, 2H), 2.06-2.21 (m, 1H), 1.18 (t, 3H), 0.74-0.87 (m, 4H)
3	^{1}H NMR (300 MHz, DMSO-d_6) 9.80 (br. s., 1H), 8.00 (s, 1H), 7.85 (d, 1H), 7.43 (d, 1H), 6.41 (s, 1H), 3.68 (s, 3H), 3.36 (s, 3H), 2.35 (q, 2H), 2.18 (br. s., 1H), 1.04 (t, 3H), 0.76 (br. s., 2H), 0.58-0.68 (m, 2H)
4	^{1}H NMR (300 MHz, DMSO-d_6) 10.42 (s, 1H), 9.62 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.71 (s, 1H), 7.05 (s, 1H), 3.76 (s, 3H), 2.73 (q, 2H), 2.09 (d, 1H), 1.19 (t, 3H), 0.80 (t, 4H).
5	^{1}H NMR (300 MHz, DMSO-d_6) 9.70 (br. s., 1H), 9.33 (br. s., 1H), 7.92 (s, 1H), 7.29 (d, 1H), 7.06 (d, 1H), 6.10-6.49 (m, 1H), 6.06 (s, 1H), 5.74 (s, 1H), 4.40 (d, 2H), 3.61 (s, 3H), 2.39 (q, 2H), 2.26 (br. s., 1H), 1.04 (t, 3H), 0.76 (br. s., 2H), 0.63 (br. s., 2H)
7	^{1}H NMR (300 MHz, DMSO-d_6) 10.23 (1 H, s), 8.57 (1 H, s), 8.42 (1 H, s), 8.09 (1 H, s), 6.58 (1 H, s), 3.76 (3 H, s), 3.40 (3 H, s), 2.46 (2 H, q), 2.15-2.08 (1H, m), 1.10 (3 H, t), 0.81 (2H, br s, 2xCH), 0.71 (2H, br s, 2xCH).

Cpd#	NMR spectrum
8	^{1}H NMR (300 MHz, DMSO-d_6) 0.53 – 0.63 (m, 2H), 0.70 – 0.78 (m, 2H), 1.08 (t, 3H), 2.16 – 2.29(m, 1H), 2.43 (q, 2H), 3.07 (s, 3H), 3.33 (s, 3H), 3.65 (s, 3H), 3.96 – 4.08 (m, 1H), 4.09 – 4.23 (m, 4H), 6.17(s, 1H), 7.35 (s, 1H), 7.95 (s, 1H), 8.38 (s, 1H), 9.68 (s, 1H).
9	^{1}H NMR (300 MHz, DMSO-d_6) 0.53 – 0.64 (m, 2H), 0.70 – 0.79 (m, 2H), 1.08 (t, 3H), 2.15 – 2.30 (m, 1H), 2.43 (q, 2H), 3.33 (s, 3H), 3.65 (s, 3H), 4.09 – 4.25 (m, 1H), 4.35 – 4.50 (m, 1H), 6.18 (s, 1H), 7.22 (s, 1H), 7.34 (s, 1H), 7.98 (s, 1H), 8.42 (s, 1H).
10	^{1}H NMR (300 MHz, DMSO-d_6) 9.61-9.76 (m, 1H), 8.29 (s, 1H), 7.93 (s, 1H), 7.58-7.73 (m, 1H), 7.43 (s, 1H), 6.13 (s, 1H), 4.12-4.32 (m, 2H), 3.59-3.68 (m, 3H), 2.95 (s, 3H), 2.44 (m, 2H), 2.16-2.29 (m, 1H), 1.09 (t, 3H), 0.57-0.92 (m, 4H)
11	^{1}H NMR (300 MHz, DMSO-d_6) 9.67 (br. s., 1H), 8.32 (s, 1H), 7.94 (s, 1H), 7.36 (s, 1H), 6.17 (s, 1H), 4.37 (s, 2H), 3.65 (s, 3H), 3.00 (s, 3H), 2.82 (s, 3H), 2.41-2.47 (m, 2H), 2.22 (br. s., 1H), 1.09 (t, 3H), 0.73 (d, 2H), 0.52-0.65 (m, 2H)
12	^{1}H NMR (300 MHz, DMSO-d_6) 10.46 (1 H, s), 8.64 (1 H, d), 8.52 (1 H, s), 7.70 (1 H, d), 7.61 (1 H, s), 6.60 (1 H, s), 3.78 (3 H, s), 2.67 (2 H, q), 2.16 (1 H, br. s), 1.12 (3 H, t), 0.84 (2 H, s), 0.80-0.75 (2 H, m).
13	1H NMR (300 MHz, $CHCl_3$-d) 8.43 (1 H, s), 7.60 (1 H, s), 7.40 (1 H, s), 7.29 (1 H, dd), 5.94 (1 H, s), 3.69 (3 H, s), 3.34 (3 H, s), 2.60 (2 H, q), 2.65-2.55 (1 H, m), 1.17 (3 H, t), 1.08-1.03 (2 H, m), 0.60-0.54 (2 H, m).
15	^{1}H NMR (300 MHz, DMSO-d_6) 10.07 (br. s., 1H), 8.31 (d, 1H), 8.25 (s, 1H), 8.13 (s, 1H), 7.51 (s, 1H), 7.42-7.48 (m, 1H), 7.03 (s, 1H), 3.75 (s, 3H), 2.72 (q, 2H), 2.13 (s, 3H), 1.18 (t, 3H)
16	^{1}H NMR (300 MHz, DMSO-d_6) 0.49 – 0.66 (m, 2H), 0.66 – 0.80 (m, 2H), 1.08 (t, 3H), 2.19 – 2.35 (m, 1H), 3.25 (s, 3H), 3.64 (s, 3H), 4.29 – 4.45 (m, 2H), 6.14 (s, 1H), 6.32 (t, 1H), 7.03 (d, 1H), 7.09 (s, 1H), 7.94 (s, 1H), 9.37 (s, 1H), 9.55 (s, 1H).
17	^{1}H NMR (300 MHz, DMSO-d_6) 9.78 (br. s., 1H), 7.97 (s, 1H), 7.81 (s, 1H), 7.59 (d, 1H), 7.49 (t, 1H), 7.20 (s, 1H), 7.13 (d, 1H), 6.46 (s, 1H), 4.12 (d, 2H), 3.66 (s, 3H), 2.86 (s, 3H), 2.65 (q, 2H), 2.12 (s, 3H), 1.14 (t, 3H)
18	^{1}H NMR (400 MHz, DMSO-d_6) 0.55 – 0.64 (m, 2H), 0.71 – 0.79 (m, 2H), 1.09 (t, 3H), 2.24 – 2.34 (m, 1H), 2.45 – 2.54 (m, 2H), 2.74 (s, 3H), 2.98 (s, 3H), 3.27 (s, 3H), 3.66 (s, 3H), 4.25 (s, 2H), 6.17 (s, 1H), 7.05 – 7.12 (m, 1H), 7.14 (s, 1H), 8.02 (s, 1H), 9.70 (s, 1H).
19	^{1}H NMR (300 MHz, DMSO-d_6) 9.77 (br. s., 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.58 (d, 1H), 7.48 (t, 1H), 7.19 (d, 1H), 7.12 (dd, 1H), 6.45 (s, 1H), 4.11 (d, 2H), 3.62-3.67 (m, 3H), 2.85 (s, 3H), 2.64 (q, 2H), 2.11 (s, 3H), 1.13 (t, 3H)
20	^{1}H NMR (300 MHz, DMSO-d_6) 9.45 (br. s., 1H), 7.97 (s, 1H), 7.78 (d, 1H), 7.72 (s, 1H), 6.39 (br. s., 1H), 3.70 (s, 3H), 3.27 (s, 3H), 2.52 (d, 2H), 1.09 (t, 3H)
21	^{1}H NMR (400 MHz, DMSO-d_6) 0.50 – 0.66 (m, 2H), 0.69 – 0.81 (m, 2H), 1.09 (t, 3H), 2.23 – 2.34 (m, 1H), 2.45 – 2.55 (m, 2H), 2.92 (s, 3H), 3.26 (s, 3H), 3.65 (s, 3H), 4.49 (s, 2H), 6.18 (s, 1H), 7.06 – 7.13 (m, 1H), 7.24 (t, 1H), 7.98 (s, 1H), 9.63 (s, 1H).
23	^{1}H NMR (300 MHz, DMSO-d_6) 10.21 (1H, s), 8.19 (1H, s), 7.39-7.35 (2H, m), 7.15-7.11 (1H, m), 7.09-7.08 (1H, m), 7.07-7.06 (1H, m), 7.01 (1H, s), 3.79 (3H, s), 2.13-2.07 (1H, m), 0.78-0.75 (2H, m), 0.71-0.67 (2H, m)
24	^{1}H NMR (300 MHz, DMSO-d_6) 10.39 (1H, s), 8.26 (1H, s), 8.05 (1H, dd), 7.77-7.71 (1H, m), 7.48 (1H, t), 7.24 (1H, s), 3.83 (3H, s), 2.06-2.01 (1H, m), 0.78-0.74 (2H, m), 0.72-0.68 (2H, m)
26	^{1}H NMR (300 MHz, DMSO-d_6) 9.82 (1 H, s), 7.92 (1 H, s), 7.84 (1 H, s), 7.12 (1 H, td), 7.02 (1 H, m), 6.13 (1 H, s), 3.64 (3 H, s), 2.60 (2 H, q), 2.20 (1 H, br. s), 1.08 (3 H, t), 0.78-0.74 (2 H, m), 0.69-0.64 (2 H, m).

Cpd#	NMR spectrum
27	^{1}H NMR (400 MHz, DMSO-d_6) 8.42 (1 H, s), 7.53 (1 H, s), 6.82-6.77 (1 H, m), 6.71 (1 H, m), 5.80 (1 H, s), 3.62 (3 H, s), 3.30 (3 H, s), 2.76 (1 H, br. s), 2.52 (2 H, q), 1.11 (3 H, t), 1.06-1.02 (2 H, m), 0.65-0.60 (2 H, m).
28	^{1}H NMR (400 MHz, DMSO-d_6) 10.04 (1 H, s), 7.94 (1 H, s), 7.82 (1 H, s), 7.52 (1 H, dd), 7.06 (1 H, dd), 6.97 (1 H, td), 6.34 (1 H, s), 3.65 (3 H, s), 2.61 (2 H, q), 2.15 (1 H, br. s), 1.11 (3 H, t), 0.80-0.70 (4 H, m).
29	^{1}H NMR (400 MHz, DMSO-d_6) 10.00 (1 H, s), 8.61 (1 H, s), 8.04 (1 H, s), 7.82 (1 H, dd), 7.70 (1 H, s), 6.59 (1 H, s), 6.26 (1 H, m), 3.72 (3 H, s), 3.32 (2 H, td), 2.08 (1 H, br. s), 0.76-0.72 (2 H, m), 0.70-0.64 (2 H, m).
30	^{1}H NMR (400 MHz, DMSO-d_6) 9.73 (1 H, s), 7.91 (1 H, s), 7.24-7.19 (2 H, m), 7.11 (1 H, td), 5.94 (1 H, s), 3.59 (3 H, s), 3.29 (3 H, s), 2.44 (2 H, q), 2.30 (1 H, br. s), 1.09 (3 H, t), 0.80-0.75 (2 H, m), 0.68-0.64 (2 H, m).
32	^{1}H NMR (400 MHz, DMSO-d_6) 10.36 (1 H, s), 8.52 (1 H, s), 7.97 (1 H, s), 7.88 (1 H, d), 7.49 (1 H, d), 6.48 (1 H, s), 6.27 (1 H, m), 3.76 (3 H, s), 3.35 (3 H, s), 3.08 (2 H, td), 2.13 (1 H, br. s), 0.86-0.80 (2 H, m), 0.77-0.72 (2 H, m).
34	^{1}H NMR (400 MHz, $CHCl_3$-d) 7.80 (1 H, s), 7.55-.748 (2 H, m), 7.41 (1 H, d), 6.46 (1 H, t), 6.25 (1 H, s), 3.76 (3 H, s), 3.44 (3 H, s), 2.31 (1 H, br. s), 1.05 (2 H, br. s), 0.69-0.64 (2 H, m).
35	^{1}H NMR (400 MHz, DMSO-d_6) 10.81 (1 H, s), 8.88 (1 H, s), 8.38 (1 H, s), 7.62 (1 H, s), 6.80 (1 H, s), 6.37 (1H, s), 3.94 (2H, d), 3.77 (3H, s), 3.40 (5H + CH3), 2.96 (3H, s), 2.73 (2H, m), 2.46 (2H, q), 2.18 (1H, m), 1.13 (3H, t), 0.83-0.89 (4H, m).
36	^{1}H NMR (400 MHz, DMSO-d_6) 9.85 (1 H, s), 8.00 (1 H, s), 7.82 (1 H, dd), 7.75 (1 H, s), 6.38 (1 H, s), 4.61 (1H, dF), 3.70 (3 H, s), 3.28 (3 H, s), 2.53 (2 H, q), 2.32 (1H, br s), 1.64-1.53 (1H, m), 1.10 (3 H, t), 0.96 (1H, br s).
38	^{1}H NMR (400 MHz, DMSO-d_6) 9.71 (1 H, s), 7.93 (1 H, s), 7.44 (1H, s), 7.37 (1 H, dd), 7.16 (1 H, d), 6.24 (1H, s), 5.99 (1H, s), 3.88 (2H, br s), 3.59 (3 H, s), 3.39 (2H, t), 3.31 (3H, s), 2.95 (3H, s), 2.64 (2H, br s), 2.44 (2H, q), 1.10 (3 H, t), 0.86-0.82 (1H, m), 0.76 (2H, br s), 0.62 (2H, br s).
39	^{1}H NMR (400 MHz, DMSO-d_6) 9.78 (1 H, s), 7.94 (1 H, s), 7.45 (1H, d), 7.38 (1 H, dd), 7.16 (1 H, d), 6.25 (1H, s), 6.01 (1H, br s), 4.60 (1H, dF) 3.88 (2H, br s), 3.61 (3 H, s), 3.40 (2H, t), 3.31 (3H, s), 2.95 (3H, s), 2.64 (2H, br s), 2.45 (2H, q), 2.30 (1H, br s), 1.64-1.50 (1H, m), 1.10 (3 H, t), 0.97 (1H, br s).
40	^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (1 H, s), 8.00 (1 H, s), 7.82 (1 H, dd), 7.75 (1 H, s), 6.38 (1 H, s), 4.61 (1H, dF), 3.70 (3 H, s), 3.28 (3 H, s), 2.53 (2 H, q), 2.32 (1H, br s), 1.64-1.54 (1H, m), 1.10 (3 H, t), 0.97 (1H, br s).
41	^{1}H NMR (400 MHz, DMSO-d_6) 9.78 (1 H, s), 8.01 (1 H, s), 7.81 (1 H, dd), 7.75 (1 H, s), 6.46 (1 H, s), 3.72 (3 H, s), 3.28 (3 H, s), 2.65 (2H, br s), 2.55 (2 H, q), 2.45 (3H, br s), 1.11 (3 H, t).
42	^{1}H NMR (400 MHz, $CHCl_3$-d) 9.28 (1 H, s), 8.53 (1 H, s), 7.78 (1 H, s), 5.81 (1 H, s), 3.93 (3 H, s), 3.56 (3 H, s), 2.98 (2H, br s), 2.89 (3H, br s&CH), 2.61 (2 H, q), 1.28 (3 H, t).
43	^{1}H NMR (400 MHz, DMSO-d_6) 9.55 (1 H, s), 8.00 (1 H, s), 7.82 (1 H, d), 7.75 (1 H, s), 6.33 (1 H, s), 5.43 (1H, s br, OH), 3.90 (2H, d), 3.71 (3H, s), 3.30 (3H, s), 2.55 (2H, q), 1.12 (3H, t).
44	^{1}H NMR (400 MHz, DMSO-d_6) 9.90 (1 H, s), 8.01 (1 H, s), 7.83 (1 H, d), 7.75 (1 H, s), 6.42 (1 H, s), 4.64-4.80 (1H, d), 3.71 (3H, s), 3.29 (3H, s), 2.55 (2H, q), 2.33 (1H, m), 1.54-1.64 (1H, m), 1.12 (3H, t), 0.97 (1H, m).
45	^{1}H NMR (400 MHz, DMSO-d_6) 9.85 (1 H, s), 8.35 (1 H, s), 7.97 (1 H, s), 7.59 (1 H, s), 6.78 (1 H, s), 6.19 (1H, s), 4.64-4.80 (1H, d), 3.96 (2H, d), 3.66 (3H, s), 3.40 (2H, t), 2.98 (3H, s), 2.74 (2H, m), 2.47 (2H, q), 2.44 (1H, m), 1.54-1.64 (1H, m), 1.13 (3H, t), 0.97 (1H, m).
46	^{1}H NMR (400 MHz, DMSO-d_6) 8.31 (1 H, s), 8.00 (1 H, s), 7.83 (1 H, d), 7.75 (1 H, s), 6.39 (1 H, s), 3.69 (3H, s), 3.29 (3H, s), 2.55 (2H, q), 1.59 (4H, s, 2*CH2), 1.12 (3H, t).

Cpd#	NMR spectrum
47	^{1}H NMR (400 MHz, DMSO-d_6) 10.02 (1 H, s), 8.56 (1 H, s), 8.06 (1 H, s), 8.02 (1 H, s), 6.49 (1 H, s), 4.68 (1H, dF), 3.71 (3 H, s), 3.40 (3 H, s), 2.46 (2 H, q), 2.31-2.24 (1H, m), 1.63-1.53 (1H, m), 1.10 (3 H, t), 1.06-0.97 (1H, m).
48	^{1}H NMR (400 MHz, DMSO-d_6) 10.44 (1H, s), 8.67 (1 H, s), 8.09 (1 H, s), 8.08 (1H, s), 7.32 (1 H, d), 7.23 (1 H, d), 6.89 (1 H, s), 4.87 (1H, dmF), 3.75 (3 H, s), 2.35 (3 H, s), 2.31 (1H, br s), 1.68 (1H, dm), 1.16 (1H, br s).
49	^{1}H NMR (400 MHz, DMSO-d_6) 10.41 (1H, s), 8.59 (1 H, s), 8.10 (1 H, s), 8.08 (1H, s), 7.33 (1 H, d), 7.29 (1 H, dd), 6.86 (1 H, s), 4.71 (1H, dF), 3.74 (3 H, s), 2.76 (2H, q), 2.32 (1H, br s), 1.67 (1H, dm), 1.17 (3H, t), 1.12 (1H, br s).
50	^{1}H NMR (400 MHz, DMSO-d_6) 9.94 (1 H, s), 7.98 (1 H, s), 7.74 (1H, s), 7.66 (1 H, d), 7.52 (1 H, d), 6.19 (1 H, s), 4.68 (1H, dF), 3.66 (3 H, s), 3.34 (3 H, s), 2.36 (1H, br s), 2.14 (3H, s), 1.59 (1H, dm), 0.98 (1H, br s).
51	^{1}H NMR (400 MHz, DMSO-d_6) 9.91 (1 H, s), 7.98 (1 H, s), 7.74 (1H, s), 7.73 (1 H, d), 7.58 (1 H, d), 6.16 (1 H, s), 4.64 (1H, dF), 3.66 (3 H, s), 3.34 (3H, s), 2.51 (2H, q), 2.39 (1H, br s), 1.60 (1H, dm), 1.10 (3H, t), 1.00 (1H, br s).
52	^{1}H NMR (400 MHz, DMSO-d_6) Diastereoisomer 1: 9.57 (1 H, s), 7.98 (1 H, s), 7.83 (1 H, d), 7.74 (1 H, s), 6.40 (1 H, s), 3.70 (3H, s), 3.27 (3H, s), 2.55 (2H, q), 1.99 (1H, m), 1.21 (1H, m), 1.11 (3H, t), 0.96 (3H, m), 0.90 (1H, m), 0.74 (1H, m).Diastereoisomer 2: 9.53 (1 H, s), 7.99 (1 H, s), 7.80 (1 H, d), 7.72 (1 H, s), 6.35 (1 H, s), 3.72 (3H, s), 3.27 (3H, s), 2.55 (2H, q), 2.19 (1H, m), 1.21 (1H, m), 1.09 (3H, t), 0.96 (3H, m), 0.90 (1H, m), 0.43 (1H, m).
53	^{1}H NMR (400 MHz, DMSO-d_6) 9.68 (1 H, s), 7.97 (1 H, s), 7.81 (1 H, d), 7.73 (1 H, s), 6.30 (1 H, s), 3.68 (3H, s), 3.28 (3H, s), 2.55 (2H, q), 2.04 (1H, s), 1.12 (3H, s), 1.09 (3H, t), 1.03 (3H, s), 0.93 (1H, m), 0.67 (1H, m).
55	^{1}H NMR (400 MHz, DMSO-d_6) 10.25 (1 H, s), 8.00 (1 H, s), 7.81 (1 H, d), 7.74 (1 H, s), 6.37 (1 H, s), 3.70 (3H, s), 3.29 (3H, s), 3.10 (1H, m), 2.55 (2H, q), 1.97 (1H, m), 1.81 (1H, m), 1.12 (3H, t).
56	^{1}H NMR (400 MHz, DMSO-d_6) 10.25 (1 H, s), 8.03 (1 H, s), 7.83 (1 H, d), 7.75 (1 H, s), 6.45 (1 H, s), 3.85 (2H, s), 3.72 (3H, s), 3.28 (3H, s), 2.55 (2H, q), 1.11 (3H, t).
57	^{1}H NMR (400 MHz, $CHCl_3$-d) 8.46 (1 H, s), 7.62 (1 H, s), 7.52 (1 H, s), 7.37 (1 H, d), 5.59 (1 H, s), 3.72 (3H, s), 3.34 (3H, s), 2.93 (2H, m), 2.55- 2.64 (4H, m, 2*CH2), 1.22 (3H, t).
59	^{1}H NMR (400 MHz, $CHCl_3$-d) 8.09 (1 H, s), 7.68 (1 H, d), 7.65 (1H, dd), 7.59 (1 H, s), 7.37 (1 H, d), 6.25 (1 H, s), 5.86 (1H, s), 5.74 (1H, s), 4.42 (1H, dF), 3.66 (3 H, s), 3.37 (3 H, s), 2.83 (1H, br s), 2.21 (3H, s), 1.97-1.87 (1H, m), 0.93 (1H, br s).
60	^{1}H NMR (400 MHz, $CHCl_3$-d) 8.56 (1 H, s), 7.71 (1 H, dd), 7.65 (1H, s), 7.58 (1 H, s), 7.42 (1 H, d), 6.14 (1 H, s), 5.85 (1H, s), 5.64 (1H, s), 4.36 (1H, dF), 3.66 (3 H, s), 3.37 (3 H, s), 2.90 (1H, br s), 2.57 (2H, q), 1.97-1.85 (1H, m), 1.17 (3H, t), 0.90 (1H, br s).
61	^{1}H NMR (400 MHz, DMSO-d_6) 9.44 (1 H, s), 7.96 (1 H, s), 7.81 (1 H, s), 7.74 (1 H, d), 6.28 (1 H, s), 3.67 (3H, s), 3.56 (3H, s), 3.28 (3H, s), 2.55 (2H, q), 1.11 (3H, t).
62	^{1}H NMR (400 MHz, DMSO-d_6) 9.94 (1 H, s), 8.59 (1 H, s), 8.02 (1 H, s), 8.00 (1 H, s), 6.51 (1 H, s), 4.54-4.75 (1H, d), 3.72 (3H, s), 3.41 (3H, s), 3.31 (3H, s), 2.55 (2H, q), 2.29 (1H, m), 1.57 (1H, d), 1.12 (3H, t), 0.99 (1H, m).
63	^{1}H NMR (400 MHz, DMSO-d_6) 10.28 (1 H, br s), 8.18 (1 H, s), 7.18 (1 H, dd), 7.06-7.02 (2 H, m), 6.93 (1 H, s), 4.66 (1 H, d), 3.78 (3 H, s), 2.54 (2 H, q), 2.32-2.22 (1 H, m), 1.63-1.52 (1 H, m), 1.12 (3 H, t), 1.07-0.98 (1 H, m).
64	^{1}H NMR (400 MHz, DMSO-d_6) 9.78 (1 H, s), 8.08 (1 H, s), 7.97 (1 H, s), 7.73 (1 H, s), 7.62 (1H, d), 7.53 (1H, s), 6.30 (1 H, s), 4.44-4.65 (1H, d), 3.68 (3H, s), 3.29 (3H, s), 2.55 (2H, q), 2.40 (1H, m), 1.58 (1H, d), 1.12 (3H, t), 0.95 (1H, m).

Cpd#	NMR spectrum
65	^{1}H NMR (400 MHz, DMSO-d_6) 9.87 (1H, s), 7.95 (1H, s), 7.42 (1H, s), 7.24 (1H, t), 7.11-7.08 (1H, m), 7.02 (1H, d), 6.07 (1H, s), 4.62 (1H, d), 3.62 (3H, s), 3.32 (3H, s), 2.48-2.39 (3H,q+m,CH), 1.65-1.55 (1H, m), 1.07 (3H, t), 1.00-0.97 (1H, m)
66	^{1}H NMR (400 MHz, DMSO-d_6) 8.36 (1 H, s), 8.00 (1 H, s), 7.82 (1 H, d), 7.75 (1 H, s), 6.37 (1 H, s), 3.68 (3H, s), 3.30 (3H, s), 2.55 (2H, q), 1.39(2H, m), 1.27 (2H, m), 1.12 (3H, t).
67	^{1}H NMR (400 MHz, DMSO-d_6) 9.81 (1 H, s), 7.91 (1 H, s), 7.88 (1 H, s), 6.59 (1 H, s), 5.95 (1 H, s), 4.81-4.65 (1 H, m), 3.59 (3 H, s), 3.30 (3 H, s), 3.05 (6 H, s), 2.35 (3 H, m), 1.61 (1 H, m), 1.08 (3 H, t). 1.01 (1 H, m).
68	^{1}H NMR (400 MHz, DMSO-d_6) 9.58 (1 H, s), 8.08 (1 H, s), 7.96 (1 H, s), 7.72 (1 H, s), 7.62 (1H, d), 7.51 (1H, s), 6.30 (1 H, s), 3.68 (3H, s), 3.28 (3H, s), 2.54 (2H, q), 2.25 (1H, m), 1.12 (3H, t), 0.72 (2H, m), 0.57 (2H, m).
70	^{1}H NMR (400 MHz, DMSO-d_6) 9.99 (1 H, s), 8.05 (1 H, s), 8.01 (1 H, s), 6.65 (1 H, s), 6.35 (1 H, s), 4.86-4.70 (1 H, m), 3.83 (3 H, s), 3.67 (3 H, s), 3.35 (3 H, s), 2.28 (2 H, q), 1.60 (1 H, m), 1.02 (3 H, t).
71	^{1}H NMR (400 MHz, DMSO-d_6) 10.14 (1 H, s), 8.58 (1 H, s), 8.07 (1 H, s), 7.93 (1 H, s), 6.69 (1 H, s), 4.88-4.68 (1 H, m), 3.78 (3 H, s), 3.43 (3 H, s), 2.37 (2 H, q), 2.25 (1 H, m), 1.58 (1 H, m), 1.46 (1 H, m), 1.04 (3 H, t).
72	^{1}H NMR (400 MHz, DMSO-d_6) 9.81 (1 H, s), 7.91 (1 H, s), 7.88 (1 H, s), 6.59 (1 H, s), 5.95 (1 H, s), 4.81-4.65 (1 H, m), 3.59 (3 H, s), 3.30 (3 H, s), 3.05 (6 H, s), 2.35 (3 H, m), 1.61 (1 H, m), 1.08 (3 H, t). 1.01 (1 H, m).
73	^{1}H NMR (400 MHz, DMSO-d_6) 10.05 (1 H, s), 8.59 (1 H, s), 8.05 (1 H, s), 6.67 (1 H, s), 4.74-4.57 (1 H, m), 3.76 (3 H, s), 3.33 (3 H, s), 2.59 (2 H, q), 2.23 (1 H, m), 1.57 (1 H, m), 1.11 (3 H, t), 1.02 (1 H, m).
74	^{1}H NMR (400 MHz, DMSO-d_6) 9.96 (1 H, s), 8.35 (1 H, s), 8.00 (1 H, s), 7.09 (1 H, s), 6.31 (1 H, s), 4.69-4.53 (1 H, m), 3.35 (3 H, s), 2.42 (3 H, s), 2.35 (2 H, q), 2.33 (1 H, m), 1.58 (1 H, m), 1.04 (3 H, t), 1.01 (1 H, m).
75	^{1}H NMR (400 MHz, DMSO-d_6) 10.08 (1 H, s), 8.38 (1 H, s), 8.07 (1 H, d), 7.20 (1 H, d), 6.52 (1 H, s), 4.77-4.60 (1 H, m), 3.71 (3 H, s), 3.39 (3 H, s), 2.39 (2 H, q), 2.33 (1 H, m), 1.62 (1 H, m), 1.00 (3 H, t).
77	^{1}H NMR (400 MHz, DMSO-d_6) 9.82 (bs, 1H), 8.41 (s, 1H), 8.10 (s, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.65 (s, 1H), 7.54 (s, 1H), 4.61 (m, 1H), 2.54 (s, 2H), 2.41 (m, 1H), 1.58 (m, 1H), 1.15 (t, 3H), 1.13 (t, 3H), 0.94 (m, 1H).
78	^{1}H NMR (400 MHz, DMSO-d_6) 10.12 (bp, 1H), 8.54 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 6.33 (s, 1H), 5.21 (d, 1H), 5.14 (dd, 1H), 5.10 (d, 1H), 4.76 (m, 1H), 4.54 (d, 2H), 3.66 (s, 3H), 2.42 (q, 2H), 2.29 (m, 1H), 1.61 (m, 1H), 1.09 (t, 3H), 1.06 (m, 1H).
79	^{1}H NMR (400 MHz, DMSO-d_6) 10.12 (bs, 1H), 8.69 (d, 1H), 8.05 (d, 1H), 8.01 (s, 1H), 6.21 (d, 1H), 4.88 (bd, 2H), 4.65 (bd, 2H), 4.06 (bs, 3H), 3.77 (s, 1H), 3.64 (s, 3H), 2.43 (q, 2H), 2.36 (m, 1H), 1.61 (m, 1H), 1.09 (t, 3H), 1.03 (m, 1H).
81	^{1}H NMR (400 MHz, DMSO-d_6) 9.89 (bp, 1H), 8.40 (s, 2H), 7.88 (s, 1H), 7.67 (s, 1H), 6.45 (s, 1H), 5.92 (s, 1H), 4.81 (m, 1H), 3.56 (s, 3H), 2.29 (m, 1H), 1.63 (m, 1H), 1.13 (t, 3H), 1.06 (m, 1H), 1.02 (t, 3H).
82	^{1}H NMR (400 MHz, DMSO-d_6) 9.73 (1 H, s br), 7.97 (1 H, s), 7.82 (1 H, s), 7.73 (1H, d), 7.39 (1H, d), 6.25 (1H, s), 3.66 (3 H, s), 3.34 (3 H, s), 2.45 (2H, q), 2.21 (1 H, m), 1.08 (3 H, t), 0.75 (2 H, m), 0.61 (2H, m).
83	^{1}H NMR (400 MHz, DMSO-d_6) 9.53 (1 H, s br), 7.99 (1 H, s), 7.74 (1 H, s), 7.69 (1 H, d), 6.43 (1H, s), 3.72 (3 H, s), 3.32 (3 H, s), 3.29 (3 H, s), 2.57 (2H, q), 2.21 (1 H, m), 1.12 (3 H, t), 0.71 (2 H, m), 0.57 (2H, m).

Cpd#	NMR spectrum
84	^{1}H NMR (400 MHz, DMSO-d_6) 9.78 (1 H, s br), 8.00 (1 H, s), 7.76 (1H, s), 7.70 (1 H, d), 6.41 (1H, s), 4.62-4.45 (1H, d), 3.72 (3 H, s), 3.33 (3 H, s), 3.29 (3 H, s), 2.60 (2H, q), 2.27 (1 H, m), 1.61-1.53 (1 H, d), 1.13 (3 H, t), 0.98 (1 H, m).
85	^{1}H NMR (400 MHz, DMSO-d_6) 9.82 (1 H, s br), 8.22 (1 H, s), 7.94 (1H, s), 7.26 (1 H, d), 6.08 (1H, s), 4.75-4.58 (1H, d), 3.63 (3 H, s), 2.49 (3 H, s), 2.41 (2H, q), 1.62-1.58 (1 H, d), 1.08 (3 H, t), 0.99 (1 H, m).
86	^{1}H NMR (400 MHz, DMSO-d_6) 9.91 (1 H, s br), 7.98 (1 H, s), 7.84 (1H, s), 7.74 (1 H, d), 7.40 (1 H, d), 6.23 (1H, s), 4.74-4.55 (1H, d), 3.66 (3 H, s), 2.45 (3 H, s), 2.41 (2H, q), 2.37 (1 H, m), 1.65-1.57 (1 H, d), 1.08 (3 H, t), 0.98 (1 H, m).
87	^{1}H NMR (400 MHz, DMSO-d_6): 9.67 (1 H, s br), 7.98 (1 H, s), 7.93 (1H, s), 7.87 (1H, s), 7.78 (1 H, d), 7.34 (1 H, s), 7.24 (1 H, d), 6.05 (1H, s), 3.61 (3 H, s), 3.33 (3 H, s), 2.46 (2H, q), 2.28 (1 H, m), 1.11 (3 H, t), 0.73 (2 H, m), 0.60 (2H, m).
88	^{1}H NMR (400 MHz, DMSO-d_6) 9.81 (1 H, s br), 7.98 (1 H, s), 7.95 (1H, s), 7.88 (1H, s), 7.78 (1 H, d), 7.37 (1 H, s), 7.25 (1 H, d), 6.06 (1H, s), 4.65-4.45 (1H, d), 3.62 (3 H, s), 1.64-1.59 (1 H, d),1.11 (3 H, t), 0.98 (1 H, m).
89	^{1}H NMR (400 MHz, DMSO-d_6) 9.82 (1 H, s br), 7.97 (1 H, s), 7.31 (1 H, t), 7.15 (1 H, d), 7.09 (1 H, d), 6.30 (1 H, s), 4.70-4.50 (1H,d), 3.66 (3 H, s), 3.33 (3 H, s), 2.67 (2H, q), 2.32 (1H, s), 1.65-1.55 (1 H, d), 1.21 (3 H, t), 1.01 (1H, s).
90	^{1}H NMR (400 MHz, DMSO-d_6) 9.83 (1 H, s br), 7.99 (1 H, s), 7.88 (1 H, d), 7.82 (1 H, dd), 7.45 (1 H, d), 6.29 (1 H, s), 4.75-4.45 (1H, d), 3.68 (3 H, s), 3.35 (3 H, s), 3.27 (3 H, s), 2.55 (2H, q), 2.36 (1H, s), 1.63-1.56 (1 H, d), 1.12 (3 H, t),0.98 (1H, s).
91	^{1}H NMR (400 MHz, DMSO-d_6) 8.23 (1 H, s br), 7.67 (1 H, s), 7.36 (1 H, s), 5.81 (1 H, s), 4.71-4.55 (1H, d), 3.77 (3 H, s), 3.44 (3 H, s), 2.74 (1H, s), 2.49 (2H, q), 2.02-1.95 (2 H, m), 1.16 (3 H, t), 1.09 (1H, s).
92	^{1}H NMR (400 MHz, DMSO-d_6) 9.96 (1 H, s br), 8.17 (1 H, s), 8.01 (1 H, s), 6.48 (s br, 1H), 4.80-4.60 (1 H, d), 3.73 (3 H, s), 3.28 (3 H, s), 2.24 (m, 1H), 2.21 (3 H, s), 1.61-1.53 (1 H, d), 1.01 (1H, s).
93	^{1}H NMR (400 MHz, DMSO-d_6) 9.74 (br. s., 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.73 (dd, 1H), 7.67 (s, 1H), 7.63 (s, 1H), 7.19 (t, 1H), 6.55 (s, 1H), 3.74 (s, 3H), 3.29 (s, 3H), 2.20-2.13 (m, 1H), 0.73-0.70 (m, 2H), 0.59-0.56 (m, 2H)
94	^{1}H NMR (400 MHz, DMSO-d_6) 9.92 (br. s., 1H), 8.17 (s, 1H), 8.01 (s, 1H), 7.74 (dd, 1H), 7.68 (s, 1H), 7.64 (s, 1H), 7.18 (t, 1H), 6.55 (s, 1H), 4.63 (br. d, 1H), 3.74 (s, 3H), 3.29 (s, 3H), 2.33 (br. s, 1H), 1.61-1.51 (m, 1H), 0.96 (br. s, 1H)
95	^{1}H NMR (400 MHz, DMSO-d_6) 9.72 (br. s., 1H), 8.54 (d, 1H), 7.97 (s, 1H), 7.68 (s, 1H), 7.59 (d, 1H), 6.25 (br. s, 1H), 4.52 (br. d, 1H), 3.67 (s, 3H), 3.29 (s, 3H), 2.81 (d, 3H), 2.56-2.53 (m, 2H), 2.41 (br. s, 1H) 1.62-1.52 (m, 1H), 1.12 (t, 3H), 0.90 (s, 1H)
96	^{1}H NMR (400 MHz, DMSO-d_6) 10.10 (br. s., 1H), 8.58 (s, 1H), 8.03 (s, 1H), 8.01 (s, 1H), 6.38 (br. s, 1H), 4.78 (br. d, 1H), 3.98-3.92 (m, 2H), 3.68 (s, 3H), 2.30-2.26 (m, 1H), 2.08 (s, 3H), 1.65-1.55 (m, 1H), 1.20-1.16 (m, 3H), 1.09-1.01 (m, 1H)
97	^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (br. s., 1H), 8.44 (t, 1H), 7.96 (s, 1H), 7.87 (s, 1H), 7.77 (dd, 1H), 7.26 (d, 1H), 6.06 (br. s, 1H), 4.76 (d, 1H), 4.63 (br. d, 1H), 3.83-3.77 (m, 1H), 3.61 (s, 3H), 3.33 (s, 3H), 3.22 (t, 2H), 2.47 (t, 2H), 2.43 (br. s, 1H), 1.63-1.50 (m, 1H), 1.11 (t, 3H), 1.08 (d, 3H), 0.96 (br. s, 1H)
98	^{1}H NMR (400 MHz, DMSO-d_6) 9.75 (br. s., 1H), 7.98 (s, 1H), 7.31 (br. s, 2H), 6.29 (br. s, 1H), 4.65-4.55 (br., 3H), 3.69 (s, 3H), 3.30 (s, 3H), 2.55-2.53 (m, 2H), 2.41 (br. s, 1H), 1.60-1.51 (m, 1H), 1.11 (t, 3H), 1.00 (br. s, 1H)

Cpd#	NMR spectrum
99	^{1}H NMR (400 MHz, DMSO-d_6) 10.54 (br. s., 1H), 9.67 (s, 1H), 8.50 (s, 1H), 8.15 (s, 1H), 7.73 (s, 1H), 7.08 (s, 1H), 5.02-4.79 (m, 1H), 3.78 (s, 3H), 2.74 (q, 2H), 2.34-2.30 (m, 1H), 1.76-1.60 (m, 1H), 1.21 (t, 3H), 1.18-1.06 (m, 1H)
100	^{1}H NMR (400 MHz, DMSO-d_6) 9.83 (bs, 1H), 8.30 (s, 1H), 8.27 (s, 1H), 8.02 (d, 1H), 7.95 (d, 1H), 7.65 (s, 1H), 6.18 (bs, 1H), 4.75-4.64 (m, 1H), 4.57-4.51 (m,1 H), 3.90 (s, 3H), 3.65(s, 3H), 3.32 (s, 3H), 2.45 (q, 2H), 1.63-1.53 (m, 1H), 1.13 (t, 3H), 0.95 (bs, 1H).
101	^{1}H NMR (400 MHz, DMSO-d_6) 9.71 (bs, 1H), 8.24 (s, 1H), 7.95 (s, 2H), 7.42 (s, 1H), 7.39 (s, 1H), 6.18 (bs, 1H), 4.76-4.38 (m, 2 H), 3.88 (s, 3H), 3.66 (s, 3H), 3.28 (s, 3H), 1.60-1.51 (m, 1H), 1.13 (q, 3H), 0.92-0.80 (m, 1H).
102	^{1}H NMR (400 MHz, DMSO-d_6) 9.83 (bs, 1H), 8.14 (s, 1H), 7.93 (s, 1H), 7.87 (d, 1H), 7.53 (d, 1H), 7.46 (dd, 1H), 7.17 (d, 1H), 6.01 (bs, 1H), 4.75-4.73 (m, 1H), 4.59-4.58 (m,1 H), 3.87 (s, 3H), 3.60 (s, 3H), 3.32 (s, 3H), 2.09 (s, 3H), 1.63-1.53 (m, 1H), 0.95 (bs, 1H).
103	^{1}H NMR (400 MHz, DMSO-d_6) 10.08 (bs, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 6.50 (s, 1H), 4.87-4.83 (m, 1 H), 4.70-4.66 (m, 1 H), 3.80 (q, 2H), 3.71 (s, 3H), 2.24 (s, 3H), 1.64-1.54 (m, 1H), 1.17 (t, 3H), 1.07-1.02 (m, 1H).
104	^{1}H NMR (400 MHz, DMSO-d_6) 10.82 (s, 1H), 9.93 (bs, 1H), 7.96 (s, 1H), 7.02 (s, 2H), 6.11 (s, 1H), 4.84-4.78 (m, 1 H), 4.68-4.62 (m, 1 H), 3.64 (s, 3H), 3.29 (s, 3H), 1.68-1.58 (m, 1H), 1.43 (d, 6H), 1.05-1.02 (m, 1H).
106	^{1}H NMR (400 MHz, DMSO-d_6) 10.07 (br. s, 1H), 8.09 (s, 1H), 8.04 (s, 1H), 6.62 (s, 1H), 4.74 (br. d, 1H), 3.75 (s, 3H), 3.30 (s, 3H), 2.25 (s, 3H), 2.24-2.18 (m, 1H), 1.62-1.51 (m, 1H), 1.07-1.00 (m, 1H).
107	^{1}H NMR (400 MHz, DMSO-d_6) 9.90 (br. s, 1H), 8.00 (s, 1H), 7.79 (d, 1H), 7.72 (s, 1H), 6.41 (s, 1H), 4.66 (br. d, 1H), 3.71 (s, 3H), 3.28 (s, 3H), 2.38-2.22 (m, 1H) 2.17 (s, 3H), 1.65-1.53 (m, 1H), 1.04-0.94 (m, 1H).
108	^{1}H NMR (400 MHz, DMSO-d_6) 9.98 (br. s, 1H), 8.00 (s, 1H), 7.79 (d, 1H), 7.72 (s, 1H), 7.73 (dd, 1H), 7.41 (d, 1H), 6.30 (s, 1H), 4.69 (br. d, 1H), 3.67 (s, 3H), 3.36 (s, 3H), 2.36-2.30 (m, 1H) 2.07 (s, 3H), 1.65-1.53 (m, 1H), 1.05-0.96 (m, 1H).
109	^{1}H NMR (400 MHz, DMSO-d_6) 10.27 (1H, s), 8.22 (1H, s), 7.87 (1H, dd), 7.75 (1H, s), 7.17 (1H, s), 4.71 (1H, d), 3.82 (3H, s), 2.60 (2H, q), 2.19 (1H, m), 1.61-1.51 (1H, m), 1.11 (3H, t), 1.06-0.97 (1H, m)
110	1H NMR (400 MHz, $CDCl_3$) 8.65 (s, 1H), 7.79 (s, 1H), 7.53 (br s, 1H), 7.43 (dd, 1H), 6.72 (s, 1H), 6.20 (br s, 1H), 5.77 (br s, 1H), 3.96 (br. d, 1H), 3.82 (s, 3H), 2.66 (q, 2H), 2.68-2.60 (m, 1H), 1.90-1.80 (m, 1H), 1.17 (t, 3H), 0.81-0.75 (m, 1H).
111	^{1}H NMR (400 MHz, DMSO-d_6) 9.92 (br. s., 1H), 8.11 (t, 1H), 8.03 (s, 1H), 8.02 (dd, 1H), 6.59 (br. s, 1H), 4.68 (br. d, 1H), 3.74 (s, 3H), 3.32 (s, 3H), 2.35-2.25 (m, 1H), 1.64-1.45 (m, 1H), 1.06-0.92 (m, 1H).
112	1H NMR (400 MHz, $CDCl_3$) 8.60 (br. s., 1H), 7.67 (t, 1H), 7.63 (s, 1H), 7.47 (dd, 1H), 6.03 (br. s, 1H), 5.70 (br. s, 1H), 4.80 (dm [two grops of multiplets]), 1H), 3.99 (s, 3H), 3.44 (s, 3H), 2.2-0.8 (br m, 3 H).
113	^{1}H NMR (400 MHz, DMSO-d_6) 10.47 (br. s., 1H), 8.25 (s, 1H), 7.81 (d, 1H), 7.64 (dd, 1H), 7.19 (s, 1H), 7.01 (d, 1H), 4.73 (br. d, 1H), 3.82 (s, 3H), 2.67 (q, 2H), 2.24-2.18 (m, 1H), 1.63-1.53 (m, 1H), 1.19 (t, 3H), 1.10-1.01 (m, 1H).
114	^{1}H NMR (400 MHz, DMSO-d_6) 10.23 (br. s., 1H), 8.22 (s, 1H), 7.94 (br. s, 1H), 7.85 (d, 1H), 7.69 (dd, 1H), 7.30 (br. s, 1H), 7.05 (s, 1H), 7.00 (d, 1H), 4.64 (br. d, 1H), 3.80 (s, 3H), 2.62 (q, 2H), 2.27-2.22 (m, 1H), 1.62-1.51 (m, 1H), 1.17 (t, 3H), 1.04-0.97 (m, 1H).
115	^{1}H NMR (400 MHz, DMSO-d_6) 10.00 (br. s, 1H), 8.12 (d, 1H), 8.05 (br. s, 1H), 7.87 (dd, 1H), 7.61 (d, 1H), 6.55 (s, 1H), 4.68 (br. d, 1H), 3.71 (s, 3H), 3.39 (s, 3H), 2.36-2.28 (m, 1H), 1.64-1.52 (m, 1H), 1.02-0.96 (m, 1H).

Cpd#	NMR spectrum
116	^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (br. s., 1H), 7.97 (s, 1H), 7.39 (br. d, 1H), 7.32 (s, 1H), 6.25 (br. s, 1H), 4.68 (br. d, 1H), 3.68 (s, 3H), 3.26 (s, 3H), 2.45-2.36 (m, 1H), 2.13 (s, 3H), 1.65-1.55 (m, 1H), 1.04-0.95 (m, 1H).
117	^{1}H NMR (400 MHz, DMSO-d_6) 9.98 (br. s., 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.20 (d, 1H), 6.22 (s, 1H), 4.74 (br. d, 1H), 3.67 (s, 3H), 3.38 (s, 3H), 2.40-2.32 (m, 1H), 2.13 (s, 3H), 1.66-1.55 (m, 1H), 1.06-0.98 (m, 1H).
118	^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (br. s., 1H), 7.93 (s, 1H), 7.36 (d, 1H), 6.99 (dd, 1H), 6.94 (d, 1H), 5.99 (br. s, 1H), 5.15 (d, 1H), 4.66 (br. d, 1H), 3.59 (s, 3H), 3.32 (s, 3H), 2.41 (q, 2H), 1.66-1.56 (m, 1H), 1.07 (t, 3H), 1.05-0.98 (m, 1H).
119	^{1}H NMR (400 MHz, DMSO-d_6) 9.86 (br. s., 1H), 8.49 (d, 1H), 8.43 (s, 1H), 8.01 (s, 1H), 6.47 (br. s, 1H), 4.55 (br. d, 1H), 3.72 (s, 3H), 3.30 (s, 3H), 2.52 (q, 2H), 2.38-2.28 (m, 1H), 1.62-1.52 (m, 1H), 1.10 (t, 3H), 1.00-0.92 (m, 1H).
120	^{1}H NMR (400 MHz, DMSO-d_6) 10.01 (br. s., 1H), 8.56 (s, 1H), 8.02 (s, 1H), 7.98 (s, 1H), 6.54 (s, 1H), 4.59 (dm [two grops of multiplets], 1H), 3.71 (s, 3H), 3.41 (s, 3H), 2.32-2.20 (m, 1H), 2.10 (s, 3H), 1.64-1.50 (m, 1H), 1.10 – 0.98 (m, 1H).
121	^{1}H NMR (500 MHz, DMSO-d6) 10.03 (br. s., 1 H), 8.02 (s, 1H), 7.88 (s, 1 H), 7.31 (s, 1 H), 7.41 (t, 1 H), 6.41 (s, 1 H), 4.68 (d, 1 H), 3.69 (s, 3 H), 3.37 (br. s., 3 H), 2.40 (q, 2 H), 2.34 (br. s., 1 H), 1.65 - 1.49 (m, 1 H), 1.06 (t, 3H), 1.03 – 0.97 (m, 1H).
122	^{1}H NMR (300 MHz, DMSO-d_6) 9.81 (br. s., 1H), 7.96 (s, H), 7.63 (br.s, 1H), 7.57 (s, 2H), 7.16 (t, 1H), 7.05 (s, 1H), 6.18 (s, 1H), 4.65 (d, 1H), 3.64 (s, 3H), 2.43 (q, 2H), 1.65-1.50 (m, 1H), 1.08 (t, 3H), 1.03 – 0.92 (m, 1H).
123	^{1}H NMR (300 MHz, DMSO-d_6) 9.94 (br. s., 1H), 8.11 (s, H), 8.01 (s, 1H), 6.56 (s, 1H), 4.67 (br d, 1H), 3.73 (s, 3H), 2.59 (q, 2H), 2.27-2.20 (m, 1H), 1.65-1.50 (m, 1H), 1.19 (t, 3H), 1.05 – 0.95 (m, 1H).
124	^{1}H NMR (300 MHz, DMSO-d_6) 9.78 (br. s., 1H), 8.10-7.90 (m, 3H), 7.68 (s, 1H), 6.46 (s, 1H), 4.59 (br d, 1H), 3.71 (s, 3H), 2.62 (q, 2H), 2.36-2.26 (m, 1H), 1.65-1.50 (m, 1H), 1.13 (t, 3H), 0.98 – 0.82 (m, 1H).
125	^{1}H NMR (400 MHz, DMSO-d_6) 9.47 (s, 1H), 8.08 (s, 1H), 8.01 (s, 1H), 6.60 (s, 1H), 3.74 (s, 3H), 3.55 (s, 3H), 3.29 (s, 3H), 2.23 (s, 3H).
126	^{1}H NMR (400 MHz, $CHCl_3$-d): 7.61 (1 H, s), 7.20-7.06 (2H, m), 5.95 (1H, s), 4.30 (1H, d), 4.20-4.16 (1H, m), 3.69 (3 H, s), 3.32 (3 H, s), 2.93 (1H, br s), 2.82-2.80 (3H, m), 2.62-2.53 (2H, m), 1.97-1.87 (1H, m), 1.83-1.83 (3H, m), 1.19-1.12 (3H, m), 0.88 (1H, br s).
127	^{1}H NMR (400 MHz, DMSO-d_6) 9.78 (br. s., 1H), 9.36 (t, 1H), 7.98 (s, 1H), 7.74 (s, 1H), 7.63 (d, 1H), 6.27 (br. s, 1H), 4.57 (br. d, 1H), 4.36 (d, 2H), 3.68 (s, 3H), 3.29 (s, 3H), 2.55 (q, 2H), 2.38 (br. s, 1H), 1.62-1.52 (m, 1H), 1.13 (t, 3H), 0.92 (br. s, 1H)
128	^{1}H NMR (400 MHz, DMSO-d_6) 10.04 (bp), 8.56 (s, 1H), 8.10 (s, 1H), 7.99 (s, 1H), 6.31 (s, 1H), 4.74 (m, 1H), 3.92 (q, 2H), 3.66 (s, 3H), 2.43 (q, 2H), 2.30 (m, 1H), 1.60 (m, 1H), 1.18 (t, 2H), 1.10 (t, 3H), 1.03 (m, 1H).
129	^{1}H NMR (400 MHz, DMSO-d_6) 9.83 (1H, s), 8.09 (1H, d), 7.99 (1H, s), 7.38 (1H, d), 6.34 (1H, s), 4.60 (1H, d), 3.70 (3H, s), 3.27 (3H, s), 2.26 (2H, q), 2.35 (1H, m), 1.63-1.53 (1H, m), 1.14 (3H, t), 1.03-0.88 (1H, m)
130	^{1}H NMR (400 MHz, DMSO-d_6) 9.96 (1 H, br s), 8.04 (1 H, s), 7.47 (1 H, s), 6.55 (1 H, s), 6.17 (1 H, s), 3.70 (3 H, s), 3.40 (3 H, s), 3.33 (3 H, s), 2.60-2.53 (1 H, m), 1.96 (2 H, q), 0.93 (3 H, t), 0.80-0.67 (4 H, m).
131	^{1}H NMR (400 MHz, DMSO-d_6) 9.45 (br. s, 1H), 8.55 (s, 1H), 8.03 (s, 1H), 7.99 (s, 1H), 6.46 (s, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.40 (s, 3H), 2.45 (q, 2H), 1.1 (t, 3H).

BIOLOGICAL EXAMPLES

Example 4. In vitro assays

4.1. JAK1 peptide assay

[0783] Recombinant human JAK1 (catalytic domain, amino acids 866-1154; catalog number PV4774) was purchased from Invitrogen. 1 ng of JAK1 was incubated with 20 nM Ulight-JAK1 (tyR[1]023) peptide (Perkin Elmer catalog number TRF0121) in kinase reaction buffer (25mM MOPS pH6.8, 0.01% Brij-35, 5mM $MgCl_2$, 2mM DTT, 7μM ATP) with or without 4 μL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 20 μL, in a white 384 Opti plate (Perkin Elmer, catalog number 6007290). After 60 min at room temperature, reactions were stopped by adding 20 μL/well of detection mixture (1 x detection buffer (Perkin Elmer, catalog number CR97-100C), 0.5nM Europium-anti-phosphotyrosine (PT66) (Perkin Elmer, catalog number AD0068), 10 mM EDTA). Readout is performed using the Envision with excitation at 320nm and measuring emission at 615 nm (Perkin Elmer). Kinase activity was calculated by subtracting relative fluorescence units (RFU) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from RFU obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

[0784] $$\text{Percentage inhibition} = \frac{(\text{RFU test compound} - \text{RFU control})}{(\text{RFU vehicle} - \text{RFU control})} * 100$$

RFU test compound = RFU determined for sample with test compound present

RFU control = RFU determined for sample with positive control inhibitor

RFU vehicle = RFU determined in the presence of vehicle

[0785] Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the JAK1 assay and the calculation of the IC_{50} for the compound. Each compound is routinely tested at concentration of 20μM followed by a 1/5 serial dilution, 10 points in a final concentration of 1% DMSO. When potency of compound series increases, more dilutions are prepared and/or the top concentration are lowered (*e.g.* 5 μM, 1 μM). The data are expressed as the average IC_{50} from the assays ± standard error of the mean.

Table IV. JAK1 IC_{50} Values of Illustrative Compounds of the invention

Cpd#	JAK1 IC_{50} (nM)
1	46
2	57
3	1
4	127
5	2
6	4
7	13; 14
8	3
9	1
10	8
11	25
12	2; 4
13	1; 3
14	81

Cpd#	JAK1 IC_{50} (nM)
15	774
16	1
17	38
18	1
19	98
20	56
21	1
22	75
23	574
24	405
25	7; 15
26	3
27	1
28	7

Cpd#	JAK1 IC_{50} (nM)
29	6
30	4
31	106
32	15
33	2
34	65
35	6
36	4
37	6
38	2
39	3
40	2; 3
41	57
42	184
43	77
44	6
45	8
46	113
47	5; 5; 5; 5; 6; 12
48	10
49	2
50	6
51	1
52	16
53	301
54	1790
55	8
56	76
57	43
58	24
59	202
60	47
61	7
62	55
63	1; 2
64	2; 2
65	3
66	231
67	13
68	2
69	19
70	10
71	16
72	64
73	1
74	798
75	115
76	4
77	3
78	16
79	3; 4
80	103
81	31

Cpd#	JAK1 IC_{50} (nM)
82	5
83	21
84	12; 12; 14; 17; 21
85	20
86	5
87	4
88	3
89	58
90	24
91	3
92	78
93	4
94	3
95	5
96	17
97	31
98	31
99	84
100	10
101	4
102	8
103	3
104	3
105	264
106	3; 3; 4; 4; 4; 5
107	7
108	11
109	9; 12; 20
110	3; 4
111	31
112	12
113	54
114	20
115	76
116	4
117	72
118	1
119	6
120	18; 19
121	21
122	73
123	1
124	7
125	11
126	8
127	1
128	6
129	7
130	139
131	15

4.2. JAK1 Ki determination assay

[0786] For the determination of Ki, different amounts of compound are mixed with the enzyme and the enzymatic reaction is followed as a function of ATP concentration. The Ki is determined by means of double reciprocal plotting of Km vs compound concentration (Lineweaver-Burk plot). 1 ng of JAK1 (Invitrogen, PV4774) is used in the assay. The substrate was 50nM Ulight-JAK-1 (TyR^1023) Peptide (Perkin Elmer, TRF0121) The reaction is performed in 25mM MOPS pH 6.8, 0.01%, 2 mM DTT, 5 mM $MgCl_2$ Brij-35 with varying concentrations of ATP and compound. Phosphorylated substrate is measured using an Eu-labeled anti-phosphotyrosine antibody PT66 (Perkin Elmer, AD0068) as described in 1.1.2. Readout is performed on the envision (Perkin Elmer) with excitation at 320 nm and emission followed at 615 nm and 665 nm.

4.3. JAK2 peptide assay

[0787] Recombinant human JAK2 (catalytic domain, amino acids 866-1154; catalog number PV4210) was purchased from Invitrogen. 0.0125mU of JAK2 was incubated with 25 nM Ulight-JAK1(tyR^1023) peptide (Perkin Elmer catalog number TRF0121) in kinase reaction buffer (25mM HEPES pH7.0, 0.01% Triton X-100, 7.5mM $MgCl_2$, 2mM DTT, 7.5μM ATP) with or without 4μL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 20 μL, in a white 384 Opti plate (Perkin Elmer, catalog number 6007290). After 60 min at room temperature, reactions were stopped by adding 20 μL/well of detection mixture (1xdetection buffer (Perkin Elmer, catalog number CR97-100C), 0.5nM Europium-anti-phosphotyrosine (PT66) (Perkin Elmer, catalog number AD0068), 10 mM EDTA). Readout is performed using the Envision with excitation at 320nm and measuring emission at 615 nm (Perkin Elmer). Kinase activity was calculated by subtracting relative fluorescence units (RFU) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from RFU obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

[0788] $$\text{Percentage inhibition} = \frac{(\text{RFU test compound} - \text{RFU control})}{(\text{RFU vehicle} - \text{RFU control})} * 100$$

RFU test compound = RFU determined for sample with test compound present

RFU control = RFU determined for sample with positive control inhibitor

RFU vehicle = RFU determined in the presence of vehicle

[0789] Dose dilution series are prepared for compound enabling the testing of dose-response effects in the JAK2 assay and the calculation of the IC_{50} for the compound. Each compound is routinely tested at concentration of 20 μM followed by a 1/5 serial dilution, 10 points in a final concentration of 1% DMSO. When potency of compound series increases, more dilutions are prepared and/or the top concentration are lowered (e.g. 5 μM, 1 μM). The data are expressed as the average IC_{50} from the assays ± standard error of the mean.

[0790] The following compounds have been tested for their activity against JAK2 and the IC_{50} values, as determined using the assays described herein, are given below.

Table V. JAK2 IC_{50} Values of Illustrative Compounds of the invention

Cpd#	JAK2 IC_{50} (nM)
1	188
2	385
3	20
4	901
5	48
6	91
7	161; 168
8	62
9	15
10	165
11	308
12	17; 22
13	18; 20
14	408
15	1780
16	9
17	167
18	3
19	231
20	234
21	3
22	716
23	2130
24	3020
25	126; 213
26	25
27	29
28	55
29	37
30	52
31	330
32	96
33	18
34	482
35	85
36	36
37	31
38	20
39	32
40	23; 42
41	261
42	1260
43	691
44	19
45	50
46	446
47	66; 83; 85; 90; 215
48	77
49	16
50	62
51	6
52	148

Cpd#	JAK2 IC_{50} (nM)
53	2770
54	4000
55	137
56	256
57	100
58	135
59	837
60	162
61	28
62	495
63	5; 10
64	15; 16
65	15
66	1300
67	143
68	14
69	219
70	107
71	247
72	176
73	18
74	3850
75	995
76	12
77	7
78	149
79	19; 26
80	684
81	154
82	41
83	68
84	65; 69; 69; 73; 101
85	187
86	39
87	37
88	34
89	119
90	155
91	45
92	532
93	41
94	34
95	61
96	138
97	418
98	110
99	784
100	82
101	19
102	170
103	26
104	34

Cpd#	JAK2 IC_{50} (nM)
105	1530
106	43; 43; 73; 73; 90; 116
107	103
108	147
109	106; 197; 321
110	57; 117
111	418
112	89
113	223
114	156
115	654
116	57
117	1100
118	12

Cpd#	JAK2 IC_{50} (nM)
119	141
120	297; 391
121	246
122	519
123	15
124	68
125	75
126	21
127	21
128	28
129	111
130	1290
131	31

4.4. JAK2 Kd determination assay

[0791] JAK2 (Invitrogen, PV4210) is used at a final concentration of 5 nM. The binding experiment is performed in 50mM Hepes pH 7.5, 0.01% Brij-35, 10mM $MgCl_2$, 1mM EGTA using 25nM kinase tracer 236 (Invitrogen, PV5592) and 2 nM Eu-anti-GST (Invitrogen, PV5594) with varying compound concentrations. Detection of tracer is performed according to the manufacturer's procedure.

4.5. JAK3 peptide assay

[0792] Recombinant human JAK3 catalytic domain (amino acids 781-1124; catalog number PV3855) was purchased from Invitrogen. 0.5 ng JAK3 protein was incubated with 2.5 µg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (25 mM Tris pH 7.5, 0.5 mM EGTA, 10mM $MgCl_2$, 2.5mM DTT, 0.5 mM Na3VO4, 5 mM b-glycerolphosphate, 0.01% Triton X-100, 1 µM non-radioactive ATP, 0.25µCi 33P-gamma-ATP (GE Healthcare, catalog number AH9968) final concentrations) with or without 5µL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 25 µL, in a polypropylene 96-well plate (Greiner, V-bottom). After 45 min at 30 °C, reactions were stopped by adding 25 µL/well of 150 mM phosphoric acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 µL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 µL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the Topcount (Perkin Elmer). Kinase activity was calculated by subtracting counts per min (cpm) obtained in the presence of a positive control inhibitor (10 µM staurosporine) from cpm obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

[0793] $$\text{Percentage inhibition} = \frac{(\text{RFU test compound} - \text{RFU control})}{(\text{RFU vehicle} - \text{RFU control})} * 100$$

RFU test compound = RFU determined for sample with test compound present

RFU control = RFU determined for sample with positive control inhibitor

RFU vehicle = RFU determined in the presence of vehicle

[0794] Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the JAK3 assay and the calculation of the IC_{50} for each compound. Each compound was

routinely tested at concentration of 20μM followed by a 1/5 serial dilution, 10 points in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 μM, 1 μM).

[0795] The following compounds have been tested for their activity against JAK3 and the IC_{50} values, as determined using the assays described herein, are given below.

Table VI. JAK3 IC_{50} Values of Illustrative Compounds of the invention

Cpd#	JAK3 IC_{50} (nM)
1	2690
2	4000
3	336
4	4000
5	217
6	211
7	878; 1700
8	403
9	41
10	1040
11	1270
12	182; 234
13	313; 324
14	4000
16	8
17	474
18	3
19	3430
20	4000
21	2
22	2770
23	4000
24	20000
25	1810; 2770
26	132
27	238
28	444
29	506
30	300
31	2040
32	750
33	310
34	2890
35	321
36	310
37	27
38	58
39	100
40	323; 375
41	3970

Cpd#	JAK3 IC_{50} (nM)
42	4000
43	4000
44	577
45	335
46	4000
47	1020; 1100; 1140; 1260; 1430; 2980
48	468
49	114
50	223
51	57
52	3280
53	20000
54	20000
55	3330
56	4000
57	3360
58	2220
59	2330
60	1660
61	466
62	4000
63	17; 37
64	154; 205
65	58
66	4000
67	1030
68	175
69	3200
70	508
71	3250
72	1360
73	283
74	4000
75	4000
76	305
77	113
78	1540
79	346; 359
80	1250
81	310

Cpd#	JAK3 IC_{50} (nM)
82	554
83	256
84	212; 221; 258; 284; 409
85	2210
86	472
87	213
88	352
89	4000
90	470
91	588
92	4000
93	325
94	309
95	468
96	3500
97	2850
98	143
99	4000
100	1400
101	131
102	1080
103	626
104	63
105	20000
106	1490; 1580; 1630; 1820; 1920

Cpd#	JAK3 IC_{50} (nM)
107	1660
108	2470
109	2630; 3420; 4000
110	590; 1020
111	3550
112	193
113	4000
114	4000
115	4000
116	617
117	4000
118	28
119	940
120	4000
121	3240
122	4000
123	293
124	1300
125	2120
126	64
127	78
128	573
129	510
130	4000
131	873

4.6. JAK3 Ki determination assay

[0796] For the determination of Ki, different amounts of compound are mixed with the enzyme and the enzymatic reaction is followed as a function of ATP concentration. The Ki is determined by means of double reciprocal plotting of Km vs compound concentration (Lineweaver-Burk plot). JAK3 (Carna Biosciences, 09CBS-0625B) is used at a final concentration of 10 ng/mL. The substrate is Poly(Glu,Tyr)sodium salt (4:1) , MW 20 000 - 50 000 (Sigma, P0275) The reaction is performed in 25mM Tris pH 7.5 , 0.01% Triton X-100 , 0.5mM EGTA, 2.5mM DTT, 0.5mM Na3VO4, 5mM b-glycerolphosphate, 10mM $MgCl_2$ with varying concentrations of ATP and compound and stopped by addition of 150 mM phosphoric acid. Measurement of incorporated phosphate into the substrate polyGT is done by loading the samples on a filter plate (using a harvester, Perkin Elmer) and subsequent washing. Incorporated 33P in polyGT is measured in a Topcount scintillation counter after addition of scintillation liquid to the filter plates (Perkin Elmer).

4.7. TYK2 peptide assay

[0797] Recombinant human TYK2 catalytic domain (amino acids 871-1187; catalog number 08-147) was purchased from Carna biosciences. 5 ng of TYK2 was incubated with 12.5 µg polyGT substrate (Sigma catalog number P0275) in kinase reaction buffer (25 mM Hepes pH 7.2, 50 mM NaCl, 0.5mM EDTA, 1mM DTT, 5mM $MnCl_2$, 10mM $MgCl_2$, 0.1% Brij-35, 0.1 µM non-radioactive ATP, 0.125 µCi

33P-gamma-ATP (GE Healthcare, catalog number AH9968) final concentrations) with or without 5μL containing test compound or vehicle (DMSO, 1% final concentration), in a total volume of 25 μL, in a polypropylene 96-well plate (Greiner, V-bottom). After 90 min at 30 °C, reactions were stopped by adding 25 μL/well of 150 mM phosphoric acid. All of the terminated kinase reaction was transferred to prewashed (75 mM phosphoric acid) 96 well filter plates (Perkin Elmer catalog number 6005177) using a cell harvester (Perkin Elmer). Plates were washed 6 times with 300 μL per well of a 75 mM phosphoric acid solution and the bottom of the plates was sealed. 40 μL/well of Microscint-20 was added, the top of the plates was sealed and readout was performed using the Topcount (Perkin Elmer). Kinase activity was calculated by subtracting counts per min (cpm) obtained in the presence of a positive control inhibitor (10 μM staurosporine) from cpm obtained in the presence of vehicle. The ability of a test compound to inhibit this activity was determined as:

[0798] $$\text{Percentage inhibition} = \frac{(\text{RFU test compound} - \text{RFU control})}{(\text{RFU vehicle} - \text{RFU control})} * 100$$

RFU test compound = RFU determined for sample with test compound present

RFU control = RFU determined for sample with positive control inhibitor

RFU vehicle = RFU determined in the presence of vehicle

[0799] Dose dilution series were prepared for the compounds enabling the testing of dose-response effects in the TYK2 assay and the calculation of the IC_{50} for each compound. Each compound was routinely tested at concentration of 20μM followed by a 1/3 serial dilution, 8 points (20μM - 6.67μM - 2.22μM - 740nM - 247nM - 82nM - 27nM - 9nM) in a final concentration of 1% DMSO. When potency of compound series increased, more dilutions were prepared and/or the top concentration was lowered (e.g. 5 μM, 1 μM).

[0800] The following compounds have been tested for their activity against TYK2; and the IC_{50} values, as determined using the assays described herein, are given below.

Table VII. TYK2 IC_{50} Values of Illustrative Compounds of the invention

Cpd#	TYK2 IC_{50} (nM)
1	126
2	211
3	7
4	149
5	77
6	68
7	26; 36
8	74
9	59
10	405
11	527
12	3; 4
13	4; 5
14	112
16	16
17	85

Cpd#	TYK2 IC_{50} (nM)
18	4
19	88
20	86
21	6
22	189
23	705
24	882
25	39; 58
26	8
27	8
28	24
29	11
30	14
31	135
32	27
33	5

Cpd#	TYK2 IC_{50} (nM)
34	163
35	23
36	4
37	6
38	4
39	5
40	2; 2
41	123
42	580
43	203
44	7
45	14
46	335
47	9; 10; 10; 10; 10; 18
48	30
49	6
50	15
51	1
52	56
53	1360
54	4000
55	53
56	100
57	47
58	51
59	249
60	53
61	8
62	200
63	2; 2
64	3; 3
65	4
66	686
67	34
68	6
69	31
70	11
71	62
72	53
73	5
74	583
75	148
76	3
77	4
78	35
79	2; 3
80	335
81	67

Cpd#	TYK2 IC_{50} (nM)
82	11
83	26
84	8; 10; 10; 10; 15
85	61
86	3
87	13
88	6
89	25
90	27
91	11
92	69
93	34
94	16
95	10
96	19
97	162
98	44
99	180
100	61
101	7
102	20
103	3
104	17
105	271
106	5; 5; 6; 9; 11
107	7
108	13
109	16; 19; 34
110	16; 32
111	51
112	68
113	79
114	157
115	52
116	4
117	166
118	12
119	25
120	43; 45
121	129
122	398
123	1
124	22
125	22
126	10
127	3
128	5
129	35

Cpd#	TYK2 IC_{50} (nM)
130	1840

Cpd#	TYK2 IC_{50} (nM)
131	25

4.8. TYK2 Kd determination assay

[0801] TYK2 (Carna Biosciences, 09CBS-0983D) is used at a final concentration of 5 nM. The binding experiment is performed in 50mM Hepes pH 7.5, 0.01% Brij-35, 10mM $MgCl_2$, 1mM EGTA using 50nM kinase tracer 236 (Invitrogen, PV5592) and 2 nM Eu-anti-GST (Invitrogen, PV5594) with varying compound concentrations. Detection of tracer is performed according to the manufacturers' procedure.

Example 5. Cellular assays

5.1. JAK1, JAK2, and TYK2 selectivity cell assays

5.1.1. Selective JAK1 cell assay, activation of STAT1 by IFNα in PBMC

[0802] Pheripheral blood mononuclear cells (PBMC) are isolated from buffy coats under sterile conditions by density gradient centrifugation using LymphoPrepTM medium (Axis-Shield) followed by 3 subsequent wash steps in PBS without Ca++ Mg++. PBMC are resuspended in plain RPMI 1640 medium containing 10% (v/v) heat inactivated FBS, 1% Pen-Strep (100 U/mL Penicilium and 100 µg/mL Streptomycin) and further cultured in a humidified incubator at 37°C 5% CO_2.

[0803] PBMC are seeded in 24 well plates at 5.0 1006 cells/well in a volume of 200 µL RPMI 1640 (Invitrogen) containing 10% (v/v) FBS and 1% Pen-Strep (Invitrogen).

[0804] PBMC are treated with test compound for 30 min at 37°C 5% CO_2. 25 µL of 10x concentrated compound dilution is added to the medium. After 30 min of test compound / vehicle pre-treatment, PBMC are stimulated for 30 min at 37°C 5% CO_2 with recombinant human IFNα (PeproTech) at final concentration of 100 ng/mL by addition of 25 µL (10x concentrated) cytokine trigger to obtain a final volume of 250 µL per well.

[0805] All compounds are tested in single starting from 20 µM followed by a 1/3 serial dilution, 8 doses in total (20 µM, 6.6 µM, 2.2 µM, 0.74 µM, 0.25 µM, 0.082 µM, 0.027 µM and 0.009 µM) in a final concentration of 0.2% DMSO.

[0806] After 30 min of cytokine stimulation, 250 µL of cell suspension is transferred to a 96-well V-bottom plate, centrifugated for 5 min at 1000 rpm to pellet cells, followed by removal of supernatant. The cell pellet is reconstituted in 100 µL 1x Lysis buffer supplemented with EDTA-free Protease Inhibitor Cocktail (Roche Applied Sciences, Product Number 11836170001) followed by sample freezing and storage at -80°C. 1x Lysis buffer is provided with the Phospho-STAT1 Elisa Kit and contains phosphatase inhibitors. Endogenous levels of phosphorylated STAT1 are quantified using a 96-well PathScan® Phospho-STAT1 (Tyr701) Sandwich ELISA Kit (Cell Signaling, Product Number #7234) according to manufacturer's instructions.

[0807] HRP activity (HRP is conjugated to the secondary antibody) is measured by addition of 100 µL of freshly prepared luminol substrate (BM Chemiluminescence ELISA Substrate (POD), Roche, Product Number 11582950001), incubation for 5 min at room temperature in the dark and measured in a Thermo Scientific Luminoskan Ascent Microplate Luminometer (integration time of 200 msec).

5.1.2. Selective JAK2 cell assay, activation of STAT5 by GM-CSF in PBMC

[0808] Pheripheral blood mononuclear cells (PBMC) are isolated from buffy coats under sterile conditions by density gradient centrifugation using LymphoPrepTM medium (Axis-Shield) followed by 3 subsequent wash steps in PBS without Ca++ Mg++. PBMC are resuspended in plain RPMI 1640 medium containing 10% (v/v) heat inactivated FBS, 1% Pen-Strep (100 U/mL Penicilium and 100 µg/mL Streptomycin) and further cultured in a humidified incubator at 37°C 5% CO_2.

[0809] PBMC are seeded in 24 well plates at 5.0E06 cells/well in a volume of 200 µL RPMI 1640 (Invitrogen) containing 10% (v/v) FBS and 1% Pen-Strep (Invitrogen).

[0810] PBMC are treated with test compound by adding 25 µL of 10x concentrated compound dilution to the medium and incubated for 30 min at 37°C 5% CO_2. Subsequently, PBMC are stimulated with recombinant human GM-CSF (PeproTech) at final concentration of 0.5 ng/mL by addition of 25 µL (10x concentrated) cytokine trigger per well to obtain a final volume of 250 µL. Cells are triggered for 30 min at 37°C 5% CO_2.

[0811] All compounds are tested in single starting from 20 µM followed by a 1/3 serial dilution, 8 doses in total (20µM, 6.6 µM, 2.2 µM, 0.74 µM, 0.25 µM, 0.082 µM, 0.027 µM and 0.009 µM) in a final concentration of 0.2% DMSO.

[0812] After 30 min of cytokine stimulation 250 µL of cell suspension is transferred to a 96-well V-bottom plate following centrifugation for 5 min at 1000 rpm to pellet cells. Cell supernatant is removed and pellet is reconstituted in 100 µL 1x Lysis buffer supplemented with EDTA-free Protease Inhibitor Cocktail (Roche Applied Sciences, Product Number 11836170001) followed by sample freezing and strorage at -80°C. 1x Lysis buffer is provided with the Phospho-STAT5 Elisa Kit and contains phosphatase inhibitors. Endogenous levels of phosphorylated STAT5 are quantified using a 96-well PathScan® Phospho-STAT5 ($TyR^{6}94$) Sandwich ELISA Kit (Cell Signaling, Product Number #7113) according to manufacturer's instructions.

[0813] HRP activity (HRP is conjugated to the secondary antibody) is measured by addition of 100 µL of freshly prepared luminol substrate (BM Chemiluminescence ELISA Substrate (POD), Roche, Product Number 11582950001), incubation for 5 min at room temperature in the dark and measured in a Thermo Scientific Luminoskan Ascent Microplate Luminometer (integration time of 200 msec).

5.2. Selective TYK2 cell assay, activation of STAT4 by IL-12 in NK-92 cells

[0814] NK-92 cells (human malignant non-Hodgkin's lymphoma, interleukin-2 (IL-2) dependent Natural Killer Cell line, ATCC #CRL-2407).

[0815] NK-92 cells are maintained in Minimum Essential Medium (MEM) Alpha medium w/o ribonucleosides and desoxyribonucleosides, 2 mM L-glutamine, 2.2 g/L sodium bicarbonate (Invitrogen, Product Number 22561-021) containing 0.2 mM myo-inositol, 0.1 mM 2-mercapto-EtOH, 0.1 mM folic acid, 12.5% heat inactivated horse serum (Invitrogen, Product Number 26050-088), 12.5% heat inactivated FBS, 1% Pen-Strep (100 U/mL Penicilium and 100 µg/mL Streptomycin) and 10 ng/mL recombinant human IL-2 (R&D Systems). IL-2 is added freshly to the medium with each medium refreshment step. Cells are cultured in a humidified incubator at 37°C 5% CO_2.

[0816] A subcultured fraction of NK-92 cells are washed once in plain medium without rhIL-2 and seeded in 24-well plates at 0.5E06 cells/well in a volume of 400 µL of plain Alpha MEM medium w/o rhIL-2 containing 0.2 mM myo-inositol, 0.1 mM 2-mercaptoethanol, 0.1 mM folic acid, 12.5% heat inactivated horse serum (Invitrogen, Product Number 26050-088), 12.5% heat inactivated FBS, 1% Pen-Strep (Invitrogen).

[0817] NK-92 cells are treated with test compounds for 30 min prior to rhIL-12 stimulation by adding 50 µL of 10x concentrated compound dilution and incubation at 37°C 5% CO_2. After 30 min of compound / vehicle pre-treatment, cells are stimulated with recombinant human IL-12 (R&D Systems, Product Number 219-IL) at final concentration of 25 ng/mL by addition of 50 µL (10x concentrated) cytokine trigger to obtain a final volume of 500 µL per well. NK-92 cells are triggered with rhIL-12 for 30 min at 37°C 5% CO_2.

[0818] All compounds are tested in single starting from 20 µM followed by a 1/3 serial dilution, 8 doses in total (20µM, 6.6 µM, 2.2 µM, 0.74 µM, 0.25 µM, 0.082 µM, 0.027 µM and 0.009 µM) in a final concentration of 0.2% DMSO.

[0819] The levels of phospho-STAT4 in rhIL-12 stimulated NK-92 cells are quantified using a flow cytometric analysis on a GalliosTM flow cytometer (Beckman Coulter). After 30 min of cytokine stimulation the cells are fixed by adding 500 µL of pre-warmed BD Cytofix Fixation Buffer (BD PhosflowTM, Product Number 554655) immediately to the wells (fix cells immediately in order to maintain phosphorylation state, rather than spinning down the cells, it is recommended to fix the cells by adding an equal volume of pre-warmed BD Cytofix Buffer to the cell suspension). Cells are incubated for 10 min at 37°C. The fixed cell fraction is resuspended (1 mL) and transferred to FACS tubes followed by a centrifugation step (300x g, 10 min) and removal of the supernatant. The cell pellet is mixed (vortex) and the cells are permeabilized by adding 1 mL of BD Phosflow Perm Buffer III (BD PhosflowTM, Product Number 558050) followed by incubation on ice for 30 min. After the permeabilization step, the cells are washed twice with BD PharmingenTM Stain Buffer (BD Pharmingen, Product Number 554656) with intermediate centrifugation at 300x g for 10 min and removal of the supernatant. The pellet (0.5E06 cells) is resuspended in 100 µL of BD PharmingenTM Stain Buffer and stained by mixing 20 µL of PE Mouse Anti-STAT4 (pY693) to the cells (BD PhosflowTM, PE Mouse Anti-STAT4 (pY693), Product Number 558249), then incubated for 30 min at room temperature in the dark. The stained cells are washed once with 2 mL of BD PharmingenTM Stain Buffer and resuspended in 500 µL of BD PharmingenTM Stain Buffer and analyzed on a GalliosTM flow cytometer (Beckman Coulter).

[0820] For all analyses, dead cells and debris are excluded by forward scatter (FSC) and side scatter (SSC). Changes in phosphorylation of STAT4 proteins following cytokine stimulation are approximated by calculating the X-median or X-mean fluorescence intensity (MFI) per cell on 100% of the gated fraction for all cytokine stimulated, test compound and unstimulated samples.

5.2.1. Results JAK1, JAK2 and TYK2 assays:

[0821] Unstimulated samples (no trigger/vehicle (0.2% DMSO) are used as a positive control (100% inhibition). As a negative control (0% inhibition), the stimulated samples (trigger/vehicle (0.2%

DMSO)) are used. The positive and negative controls are used to calculate Z' and 'percent inhibition (PIN)' values.

[0822] Percentage inhibition is calculated from

[0823] Percentage inhibition=(RCLU(trigger/veh) – RCLU(test compound))/(RCLU(trigger/veh) – RCLU(no trigger/veh))*100

wherein

RCLU(trigger/veh): Relative Chemilumescent signal determined in presence of vehicle and trigger

RCLU(test compound): Relative Chemiluminescent signal determined in presence of test compounds)

RCLU(no trigger/veh): Relative Chemiluminescent signal determined in presence of vehicle without trigger.

[0824] In case the readout signal is expressed as X-mean values (flow cytometric analysis of pSTAT4 levels in cytokine stimulated NK-92 cells), the RCLU is replaced by X-mean value.

[0825] PIN values are plotted for compounds tested in dose-response and EC_{50} values are derived using GraphPad Prism Software applying non-linear regression (sigmoidal) curve fitting.

Table VIII. JAK1 cellular selectivity values of illustrative compounds of the invention

Cpd#	JAK1 IC_{50} (nM)
47	87
61	44
64	200
68	145
70	90
79	>2220
84	98; 130
86	<27
90	704
95	>2220
96	136
100	141

Cpd#	JAK1 IC_{50} (nM)
101	652
103	108
104	170
106	45; 69
107	147
108	<82
109	119
120	<232
123	<9.1
125	251
126	137
127	129

Table IX. JAK2 cellular selectivity values of illustrative compounds of the invention

Cpd#	JAK2 IC_{50} (nM)
40	>2220
47	2630
61	775
79	>6670
84	>2220
86	231
88	890
90	>2220
94	1770
95	>6670
96	>6670
100	>2220
101	1220

Cpd#	JAK2 IC_{50} (nM)
103	347
104	1190
106	>2220; >6670
107	>6670
108	>2220
109	>2220
110	615
120	>13300
123	2590
125	>6670
126	525
127	1430

Table X. TYK2 cellular selectivity values of illustrative compounds of the invention

Cpd #	TYK2 IC_{50} (nM)
7	948

Cpd #	TYK2 IC_{50} (nM)
40	214

Cpd #	TYK2 IC_{50} (nM)
47	591
61	146
79	>20000
84	442; 774
86	<82
88	987
90	746
94	1510
95	>20000
96	601
100	>247
101	914

Cpd #	TYK2 IC_{50} (nM)
103	219
104	220
106	226; 310
107	457
108	69.6
109	294
110	498
120	<338
123	<82.3
125	179
126	463
127	>6670

5.3. JAK1 mutations in lung cancer and hepatocellular carcinoma cell lines assay.

5.3.1. JAK1 mutation induced constitutive signaling

[0826] Cancer cell lines with and without JAK1 mutations (Table I – Lung cancer cell lines) are cultured with or without serum for 4-6 h, stimulated or not with a cytokine cocktail (INFγ, IL_2, IL4 and IL6) for 5, 10, 30 and 45 min. The phosphorylation of JAK1, STAT1, STAT3 and STAT5 are evaluated by immunoblot (Cell Signaling antibodies).

5.3.2. Targeting JAK1 mutants using JAK inhibitors

5.3.2.1. JAK-STAT pathway phosphorylation:

[0827] Cancer cell lines with and without JAK1 mutations are cultured in the presence or absence of different concentrations of JAK inhibitors. Cells are analyzed at 24 and 48 h for effective JAK-STAT pathway inhibition by immunoblot.

Table XI. Illustrative lung cancer cell lines

Gene	Cell line	Tissue	Change	Protein domain	Present in primary tissue
JAK1	NCIH1915	Lung	I62V	FERM	_
JAK1	SQ1	Lung	N226S	FERM	_
JAK1	HCC4006	Lung	S383G	FERM	_
JAK1	NCIH2066	Lung	L423V	Interdomain (FERM and SH2)	–
JAK1	NCIH1793	Lung	H525Y	SH2	_
JAK1	HCC95	Lung	N833S	Protein kinase 1	Yes
JAK1	VMRCLCD	Lung	E223*	_	_
JAK1	NCIH1563	Lung	Q161*	_	_
WT JAK1	A549	Lung	_	_	_
JAK1 -/-	U4C	Fibrosarcoma	_	_	_

*: truncation

5.3.2.2. Cell viability

[0828] 2D-assay: Cancer cell lines with and without JAK1 mutations are cultured in the presence or absence of increasing concentrations of JAK inhibitors. After 48-72 h, cell viability is measured using the Cell Titer-Glo Luminescent cell viability assay (Promega) or MTT assay. Alternatively, cancer cell lines

at different culture time points with a fix concentration of JAK inhibitor are analyzed for cell viability using the Cell Titer-Glo Luminescent cell viability assay (Promega) or MTT assay.

[0829] 3D-assay: Cancer cell lines with and without JAK1 mutations are seeded in semi-solid agar medium. Formation of multi-cellular colonies is measured by determining cell viability using a fluorescent dye at different culture time points. Addition of potential inhibitors after cell seeding allows for the analyses of anti-tumorigenic effects.

5.3.3. Investigating human JAK1 mutations in murine Ba/F3 cells

[0830] (Kan et al., 2013; Staerk et al., 2005; Zenatti et al., 2011)

[0831] Construction of JAK1 expression vectors: Wild type and mutant human JAK1 sequences are cloned into retroviral vectors and clones verified by sequencing.

[0832] Retroviral infection of Ba/F3 cells: Ba/F3 cells are infected with retroviral supernatants produced in 293T cells.

[0833] Ba/F3 cells expressing human WT or mutated JAK1 are cultured with or without IL-3 for 4h and phosphorylation of the JAK-STAT pathway evaluated by immunoblot.

[0834] The transforming potential of JAK1 mutations is assessed by measuring the ability of each mutation to induce autonomous growth when expressed in cytokine-dependent Ba/F3 cells. Cell growth is assessed in the absence of the cytokine IL-3.

[0835] Mutant JAK1 transduced Ba/F3 cell lines are assessed for their sensitivity to the JAK inhibitors by culturing them in the presence or absence of increasing concentrations of JAK inhibitors. After 48-72 h, cell viability is measured using the Cell Titer-Glo Luminescent cell viability assay (Promega) or MTT assay. Alternatively, cancer cell lines at different culture time points with a fix concentration of JAK inhibitor are analyzed for cell viability using the Cell Titer-Glo Luminescent cell viability assay (Promega) or MTT assay.

5.3.4. In vivo tumorigenic potential of JAK1 mutations

5.3.4.1. Xenograft model:

[0836] Mutant JAK1 expressing cells are injected subcutaneously in CD1 nu/nu mice or Rag1−/− mice and evaluated for tumor progression. Subcutaneous tumor volume growth curves are established. The transplantability of primary tumors into secondary recipient animals is determined.

5.3.4.2. PDX model.

[0837] Patient-Derived Xenografts (PDXs) are based on the transfer of primary tumors (containing JAK1 mutations) directly from the patient into an immunodeficient mouse. To accomplish this, patient tumors must be obtained fresh from surgery, at which point they are mechanically or chemically digested, with a small portion saved as a primary stock and established in a NOD-SCID mouse. PDX models are maintained by passaging cells directly from mouse to mouse once the tumor burden becomes too high. Tumors can be engrafted heterotopically (implanting tumors into the subcutaneous flank of a mouse) or orthotopically (direct implantation to the mouse organ of choice).

[0838] The phosphorylation of JAK1, STAT1, STAT3 and STAT5 in primary and secondary tumors are evaluated by immunoblot.

5.4. PBL Proliferation assay

[0839] Human peripheral blood lymphocytes (PBL) are stimulated with IL-2 and proliferation is measured using a BrdU incorporation assay. The PBL are first stimulated for 72 h with PHA to induce IL-2 receptor, then they are fasted for 24 h to stop cell proliferation followed by IL-2 stimulation for another 72 h (including 24h BrdU labeling). Cells are preincubated with test compounds 1 h before IL-2 addition. Cells are cultured in RPMI 1640 containing 10% (v/v) FBS.

5.5. Human whole blood assay (hWBA)

5.5.1. Stimulation protocol

[0840] A flow cytometry analysis is performed to establish JAK1 over JAK2 compound selectivity ex vivo using human whole blood. Therefore, blood is taken from human volunteers who gave informed consent. Blood is then equilibrated for 30 min at 37°C under gentle rocking, then aliquoted in Eppendorf tubes. Compound is added at different concentrations and incubated at 37°C for 30 min under gentle rocking and subsequently stimulated for 20 min at 37°C under gentle rocking with interleukin 6 (IL-6) for JAK1-dependent pathway stimulation, Interferon alpha (IFNα) for JAK1/TYK2 pathway stimulation, interleukin 2 (IL-2) for JAK1/JAK3 pathway stimulation or GM-CSF for JAK2-dependent pathway stimulation. Phospho-STAT1 (for IL-6- and IFNα-stimulated cells) and phospho-STAT5 (for IL-2- and GM-CSF-stimulated cells) levels are then evaluated using FACS analysis.

5.5.2. Phospho–STAT Assays

5.5.2.1. Preparation of reagents

[0841] The 5X Lyse/Fix buffer (BD PhosFlow, Cat. no 558049) is diluted 5-fold with distilled water and pre-warmed at 37°C. The remaining diluted Lyse/Fix buffer is discarded.

[0842] 10 µg rhIL-6 (R&D Systems, Cat no 206-IL) is dissolved in 1 mL of PBS + 0.1% BSA to obtain a 10 µg/mL stock solution. The stock solution is aliquoted and stored at -80°C.

[0843] 10 µg rhIL-2 (R&D Systems, Cat no 202-IL) is dissolved in 1 mL of PBS + 0.1% BSA to obtain a 10 µg/mL stock solution. The stock solution is aliquoted and stored at -80°C.

[0844] 5 µg rhGM-CSF (AbCys S.A., Cat no P300-03) is dissolved in 12.5 mL of PBS + 0.1% BSA to obtain a 400 ng/mL stock solution. The stock solution is stored aliquoted at -80°C.

[0845] A 3-fold dilution series of the compound is prepared in DMSO (10 mM stock solution). Control-treated samples received DMSO instead of compound. All samples are incubated with a 1% final DMSO concentration.

5.5.2.2. Incubation of blood with compound and stimulation with triggers

[0846] Human blood is collected in heparinized tubes. The blood is divided in aliquots of 148.5µL. Then, 1.5 µL of the test compound dilution is added to each blood aliquot and the blood samples are incubated for 30 min at 37°C under gentle rocking. One and a half microliter of 10-fold diluted IL-6 stock

solution, 1.5 µL of uIFNα (PBL Biomedical, Cat no 11200-1) stock solution, 1.5 µL of 25-fold diluted IL-2 stock solution or 1.5 µL of 200-fold dilution of the GM-CSF stock solution is added to the blood samples and samples are incubated at 37°C for 20 min under gentle rocking.

5.5.2.3. White blood cell preparation

[0847] At the end of the stimulation period, 3 mL of 1X pre-warmed Lyse/Fix buffer is immediately added to the blood samples, vortexed briefly and incubated for 15 min at 37°C in a water bath in order to lyse red blood cells and fix leukocytes.

[0848] Tubes are centrifuged for 5 min at 400xg at 4°C. The cell pellet is washed with 3 mL of cold 1X PBS, and after centrifugation the cell pellet is resuspended in 100 µL of ice-cold 1X PBS and 900µL ice-cold 100% MeOH is added. Cells are then incubated at 4°C for 30 min for permeabilization.

[0849] Permeabilized cells are then washed with 1X PBS containing 3% BSA and finally resuspended in 80 µL of 1X PBX containing 3% BSA.

5.5.2.4. Cell labeling

[0850] 20µL of PE mouse anti-STAT1 (pY701) or PE mouse IgG2aκ isotype control antibody (BD Biosciences, Cat. no 612564 and 559319, respectively) and APC-conjugated anti-CD4 antibody or control APC-conjugated isotype antibody (BD Biosciences, Cat. no 555349 and 555751, respectively) are added to IL-6-and IFNα-stimulated tubes and mixed, then incubated for 20 min at 4°C, in the dark.

[0851] 20µL of PE mouse anti-STAT5 (pY694) or PE mouse IgG1κ isotype control antibody (BD Biosciences, Cat. no 612567 and 554680, respectively) and APC-conjugated anti-CD4 antibody or control APC-conjugated isotype antibody (BD Biosciences, Cat. no 555349 and 555751, respectively) are added to IL-2-stimulated tubes, mixed then incubated for 20 min at 4°C, in the dark.

[0852] 20µL of PE mouse anti-STAT5 (pY694) or PE mouse IgG1κ isotype control antibody (BD Biosciences, Cat. no 612567 and 554680, respectively) and APC mouse anti CD33 antibody (BD Biosciences #345800) or control APC mouse IgG1 isotype antibody (BD Biosciences Cat. no 345818) are added to GM-CSF-stimulated tubes, mixed then incubated for 20 min at 4°C, in the dark.

[0853] Cells are then washed once with 1X PBS and analyzed on a FACSCanto II flow cytometer (BD Biosciences).

5.5.2.5. Fluorescence analysis on FACSCanto II

[0854] 50,000 total events are counted and Phospho-STAT1 positive cells are measured after gating on CD4+ cells, in the lymphocyte gate for IL-6- and IFNα-stimulated cells. Phospho-STAT5 positive cells are measured after gating on CD4+ cells, in the lymphocyte gate for IL-2-stimulated cells. Phospho-STAT5 positive cells are measured after gating on CD33+ cells. Data are analyzed using the FACSDiva software and the percentage of inhibition of IL-6 or IFNα stimulation calculated is from the percentage of positive cells for phospho-STAT1 on CD4+ cells. For the IL-2 stimulated cells, data are analyzed using the FACSDiva software and the percentage of inhibition of IL-2 stimulation is calculated from the percentage of positive cells for phospho-STAT1 on CD4+ cells. For the GM-CSF stimulated cells, the

percentage of inhibition of GM-CSF stimulation is calculated from the percentage of positive cells for phosphor-STAT5 on CD33+ cells.

Table XII. Human whole blood JAK1 selectivity (Trigger IFNα)

Cpd#	JAK1 IC_{50} (nM)
12	1580
47	517
79	1630
84	588
95	2220
96	860

Cpd#	JAK1 IC_{50} (nM)
106	193; 533
108	894
109	1070
120	855
123	288
127	1770

Table XIII. Human whole blood JAK1 selectivity (Trigger IL6)

Cpd#	JAK1 IC_{50} (nM)
7	1480
8	874
12	2480
29	1080
47	869
61	1960

Cpd#	JAK1 IC_{50} (nM)
70	1350
88	1610
100	3720
106	494
110	506

Table XIV. Human whole blood JAK2 selectivity

G#	JAK2 IC_{50} (nM)
7	>19200
29	>10000
47	8780, >5840
61	>14800
64	3490
68	2600
70	6470
79	3080

G#	JAK2 IC_{50} (nM)
84	19900
96	11500
106	>13100
109	>30000
110	>10000
123	3030
127	>13500

Example 6. In vivo models

6.1. CIA model

6.1.1. Materials

[0855] Completed Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) were purchased from Difco. Bovine collagen type II (CII), lipopolysaccharide (LPS), and Enbrel was obtained from Chondrex (Isle d'Abeau, France); Sigma (P4252, L'Isle d'Abeau, France), Whyett (25mg injectable syringe, France) Acros Organics (Palo Alto, CA), respectively. All other reagents used were of reagent grade and all solvents were of analytical grade.

6.1.2. Animals

[0856] Dark Agouti rats (male, 7-8 weeks old) were obtained from Harlan Laboratories (Maison-Alfort, France). Rats were kept on a 12 h light/dark cycle (0700 - 1900). Temperature was maintained at 22°C, and food and water were provided ad libitum.

6.1.3. Collagen induced arthritis (CIA)

[0857] One day before the experiment, CII solution (2 mg/mL) was prepared with 0.05 M acetic acid and stored at 4°C. Just before the immunization, equal volumes of adjuvant (IFA) and CII were mixed by a homogenizer in a pre-cooled glass bottle in an ice water bath. Extra adjuvant and prolonged homogenization may be required if an emulsion is not formed. 0.2 mL of the emulsion was injected intradermally at the base of the tail of each rat on day 1, a second booster intradermal injection (CII solution at 2 mg/mL in CFA 0.1 mL saline) was performed on day 9. This immunization method was modified from published methods (Jou et al., 2005; Sims et al., 2004).

6.1.4. Study design

[0858] The therapeutic effects of the compounds were tested in the rat CIA model. Rats were randomLy divided into equal groups and each group contained 10 rats. All rats were immunized on day 1 and boosted on day 9. Therapeutic dosing lasted from day 16 to day 30. The negative control group was treated with vehicle (MC 0.5%) and the positive control group with Enbrel (10 mg/kg, 3x week. s.c.). A compound of interest was typically tested at 3 doses, e.g. 3, 10, 30 mg/kg, p.o.

6.1.5. Clinical assessment of arthritis

[0859] Arthritis is scored according to reported methods (Khachigian, 2006; Lin et al., 2007; Nishida et al., 2004). The swelling of each of the four paws is ranked with the arthritic score as follows: 0-no symptoms; 1-mild, but definite redness and swelling of one type of joint such as the ankle or wrist, or apparent redness and swelling limited to individual digits, regardless of the number of affected digits; 2-moderate redness and swelling of two or more types of joints; 3-severe redness and swelling of the entire paw including digits; 4-maximally inflamed limb with involvement of multiple joints (maximum cumulative clinical arthritis score 16 per animal).

[0860] To permit the meta-analysis of multiple studies the clinical score values were normalised as follows:

[0861] AUC of clinical score (AUC score): The area under the curve (AUC) from day 1 to day 14 was calculated for each individual rat. The AUC of each animal was divided by the average AUC obtained for the vehicle in the study from which the data on that animal was obtained and multiplied by 100 (i.e. the AUC was expressed as a percentage of the average vehicle AUC per study).

[0862] Clinical score increase from day 1 to day 14 (End point score): The clinical score difference for each animal was divided by the average clinical score difference obtained for the vehicle in the study from which the data on that animal was obtained and multiplied by 100 (i.e. the difference was expressed as a percentage of the average clinical score difference for the vehicle per study).

6.1.6. Change in body weight (%) after onset of arthritis

[0863] Clinically, body weight loss is associated with arthritis (Rall and Roubenoff, 2004; Shelton et al., 2005; Walsmith et al., 2004). Hence, changes in body weight after onset of arthritis can be used as a non-specific endpoint to evaluate the effect of therapeutics in the rat model.

[0864] The change in body weight (%) after onset of arthritis was calculated as follows:

[0865] Mice: $$\frac{\text{Body Weigh t}_{(\text{week6})} - \text{Body Weigh t}_{(\text{week5})}}{\text{Body Weigh t}_{(\text{week5})}} \times 100\%$$

[0866] Rats: $$\frac{\text{Body Weight}_{(\text{week4})} - \text{Body Weight}_{(\text{week3})}}{\text{Body Weight}_{(\text{week3})}} \times 100\%$$

6.1.7. Radiology

[0867] X-ray photos were taken of the hind paws of each individual animal. A random blind identity number was assigned to each of the photos, and the severity of bone erosion was ranked by two independent scorers with the radiological Larsen's score system as follows: 0- normal with intact bony outlines and normal joint space; 1- slight abnormality with any one or two of the exterior metatarsal bones showing slight bone erosion; 2-definite early abnormality with any 3 to 5 of the exterior metatarsal bones showing bone erosion; 3-medium destructive abnormality with all the exterior metatarsal bones as well as any one or two of the interior metatarsal bones showing definite bone erosions; 4-severe destructive abnormality with all the metatarsal bones showing definite bone erosion and at least one of the inner metatarsal joints completely eroded leaving some bony joint outlines partly preserved; 5-mutilating abnormality without bony outlines. This scoring system is a modification from (Bush et al., 2002; Jou et al., 2005; Salvemini et al., 2001; Sims et al., 2004).

6.1.8. Histology

[0868] After radiological analysis, the hind paws of mice were fixed in 10% phosphate-buffered formalin (pH 7.4), decalcified with rapid bone decalcifiant for fine histology (Laboratories Eurobio) and embedded in paraffin. To ensure extensive evaluation of the arthritic joints, at least four serial sections (5 µm thick) were cut and each series of sections were 100 µm in between. The sections were stained with hematoxylin and eosin (H&E). Histologic examinations for synovial inflammation and bone and cartilage damage were performed double blind. In each paw, four parameters were assessed using a four-point scale. The parameters were cell infiltration, pannus severity, cartilage erosion and bone erosion. Scoring was performed according as follows: 1-normal, 2-mild, 3-moderate, 4-marked. These four scores are summed together and represented as an additional score, namely the 'RA total score'.

6.1.9. Micro-computed tomography (µCT) analysis of calcaneus (heel bone):

[0869] Bone degradation observed in RA occurs especially at the cortical bone and can be revealed by µCT analysis (Oste et al., 2007; Sims et al., 2004). After scanning and 3D volume reconstruction of the calcaneus bone, bone degradation is measured as the number of discrete objects present per slide, isolated in silico perpendicular to the longitudinal axis of the bone. The more the bone is degraded, the more discrete objects are measured. 1000 slices, evenly distributed along the calcaneus (spaced by about 10.8 µm), are analyzed.

6.1.10. Steady State PK

[0870] At day 7 or 11, blood samples were collected at the retro-orbital sinus with lithium heparin as anti-coagulant at the following time points: predose, 1, 3 and 6 h. Whole blood samples were centrifuged

and the resulting plasma samples were stored at -20°C pending analysis. Plasma concentrations of each test compound were determined by an LC-MS/MS method in which the mass spectrometer was operated in positive electrospray mode. Pharmacokinetic parameters were calculated using Winnonlin® (Pharsight®, United States) and it was assumed that the predose plasma levels were equal to the 24 h plasma levels.

6.2. Oncology models

[0871] In vivo models to validate efficacy of small molecules towards JAK2-driven myleoproliferative diseases are described (Geron et al., 2008; Wernig et al., 2008).

6.3. Mouse IBD model

[0872] In vitro and in vivo models to validate efficacy of small molecules towards IBD are described (Wirtz et al., 2007).

6.4. Mouse Asthma model

[0873] In vitro and in vivo models to validate efficacy of small molecules towards asthma are described (Ip et al., 2006; Kudlacz et al., 2008; Nials and Uddin, 2008; Pernis and Rothman, 2002).

6.5. Murine model of psoriatic-like epidermal hyperplasia induced by intradermal injections of IL22 or IL23

6.5.1. Materials

[0874] Mouse recombinant IL22 (582-ML-CF), carrier free is provided by R&D systems. Mouse recombinant IL23, carrier free (14-8231, CF) is provided by e-Bioscience.

6.5.2. Animals

[0875] Balb/c mice (female, 18-20g body weight) are obtained from CERJ (France). Mice are kept on a 12 h light/dark cycle (07:00 – 19:00). Temperature is maintained at 22°C, food and water are provided ad libitum.

6.5.3. Study design

The design of the study is adapted from Rizzo et al., 2011.

[0876] On the first day (D1), the mice are shaved around the two ears.

[0877] For 4 consecutive days (D1 to D4), the mice received a daily intradermal dose of mouse recombinant IL22 or IL23 (1µg/20µL in PBS/0.1% BSA) in the right pinna ear and 20µL of PBS/0.1%BSA in the left pinna ear under anesthesia induced by inhalation of isoflurane.

[0878] From D1 to D5, mice are dosed with test-compound (10, 30, or 100 mg/kg, po, qd in MC 0.5%), 1h prior IL23/IL22 injection or with vehicle.

6.5.4. Assessment of disease

[0879] The thickness of both ears is measured daily with an automatic caliper. Body weight is assessed at initiation and at sacrifice. On fifth day, 2 hrs after the last dosing, the mice are sacrificed. The pinnae of the ear are cut, excluding cartilage. The pinnae are weighed and then, placed in vial containing 1 mL of RNAlater solution or in formaldehyde.

[0880] At D4, blood samples are also collected from the retro-orbital sinus for PK profile just before dosing (T0) and 1h, 3h, 6h post-dosing.

[0881] There are 8 mice per group. The results are expressed as mean ± sem and statistical analysis is performed using one-way Anova followed by Dunnett's post-hoc test versus IL22 or IL23 vehicle groups.

6.5.5. Histology

[0882] After sacrifice, ears are collected and fixed in 3.7% formaldehyde before embedding in paraffin. Two µm thick sections are done and stained with hematoxylin and eosin. Ear epidermis thickness is measured by image analysis (Sis'Ncom software) with 6 images per ear captured at magnification x20. Data are expressed as mean ± sem and statistical analysis is performed using one-way Anova followed by Dunnett's post-hoc test versus IL22 or IL23 vehicle groups.

6.5.6. RNA extraction, RT-PCR and real-time PCR

[0883] IL-17a, IL-22, IL-1β, LCN2 and S100A9 transcript levels in ear tissue are determined using real-time quantitative PCR.

Example 7. Pharmacokinetic, ADME and Toxicity Assays

7.1. Thermodynamic solubility

[0884] The test compound is added to 0.2M phosphate buffer pH 7.4 or 0.1M citrate buffer pH 3.0 at a concentration of 1 mg/mL in a glass vial.

[0885] The samples are rotated in a Rotator drive STR 4 (Stuart Scientific, Bibby) at speed 3.0 at room temperature for 24 h.

[0886] After 24 h, 800 µL of the sample is transferred to an eppendorf tube and centrifuged 5 min at 14000rpm. 200 µL of the supernatant of the sample is then transferred to a MultiscreenR Solubility Plate (Millipore, MSSLBPC50) and the supernatant is filtered (10-12" Hg) with the aid of a vacuum manifold into a clean Greiner polypropylene V-bottom 96 well plate (Cat no.651201). 5 µL of the filtrate is diluted into 95 µL (F20) of the same buffer used to incubate in the plate containing the standard curve (Greiner, Cat no.651201).

[0887] The standard curve for the compound is prepared freshly in DMSO starting from a 10mM DMSO stock solution diluted factor 2 in DMSO (5000µM) and then further diluted in DMSO up to 19.5µM. 3µL of the dilution series as from 5000µM is then transferred to a 97µL acetonitrile-buffer mixture (50/50). The final concentration range is 2.5 to 150 µM.

[0888] The plate is sealed with sealing mats (MA96RD-04S, www.kinesis.co.uk) and samples are measured at room temperature on LC-MS (ZQ 1525 from Waters) under optimized conditions using Quanoptimize to determine the appropriate mass of the molecule.

[0889] The samples are analyzed on LC-MS with a flow rate of 1 mL/min. Solvent A is 15 mM ammonia and solvent B is acetonitrile. The sample is run under positive ion spray on an XBridge C18 3.5µM (2.1 x 30mm) column, from Waters. The solvent gradient has a total run time of 2 min and ranges from 5% B to 95% B.

[0890] Peak areas are analyzed with the aid of Masslynx software package and peak areas of the samples are plotted against the standard curve to obtain the solubility of the compound.

[0891] Solubility values are reported in µM or µg/mL.

7.2. Aqueous Solubility

[0892] Starting from a 10mM stock in DMSO, a serial dilution of the compound is prepared in DMSO. The dilution series is transferred to a 96 NUNC Maxisorb plate F-bottom (Cat no. 442404) and 0.1M phosphate buffer pH7.4 or 0.1M citrate buffer pH3.0 at room temperature is added.

[0893] The final concentration ranges from 300µM to 18.75µM in 5 equal dilution steps. The final DMSO concentration does not exceed 3%. 200µM Pyrene is added to the corner points of each 96 well plate and serves as a reference point for calibration of Z-axis on the microscope.

[0894] The assay plates are sealed and incubated for 1 h at 37°C while shaking at 230 rpm. The plates are then scanned under a white light microscope, yielding individual pictures of the precipitate per concentration. The precipitate is analyzed and converted into a number with a software tool which can be plotted onto a graph. The first concentration at which the compound appears completely dissolved is the concentration reported; however the true concentration lies somewhere between this concentration and one dilution step higher.

[0895] Solubility values mesured according to this protocol are reported in µg/mL.

7.3. Plasma Protein Binding (Equilibrium Dialysis)

[0896] A 10 mM stock solution of the compound in DMSO is diluted with a factor 5 in DMSO. This solution is further diluted in freshly thawed human, rat, mouse or dog plasma (BioReclamation INC) with a final concentration of 5 µM and final DMSO concentration of 0.5% (5.5µL in 1094.5µL plasma in a PP-Masterblock 96well (Greiner, Cat no. 780285))

[0897] A Pierce Red Device plate with inserts (ThermoScientific, Cat no. 89809) is prepared and filled with 750µL PBS in the buffer chamber and 500µL of the spiked plasma in the plasma chamber. The plate is incubated for 4 h at 37°C while shaking at 230rpm. After incubation, 120 µL of both chambers is transferred to 360µL acetonitrile in a 96-well round bottom, PP deep-well plates (Nunc, Cat no. 278743) and sealed with an aluminum foil lid. The samples are mixed and placed on ice for 30 min. This plate is then centrifuged 30 min at 1200 rcf at 4°C and the supernatant is transferred to a 96 v-bottom PP plate (Greiner, 651201) for analysis on LC-MS.

[0898] The plate is sealed with sealing mats (MA96RD-04S) of www.kinesis.co.uk and samples are measured at room temperature on LC-MS (ZQ 1525 from Waters) under optimized conditions using Quanoptimize to determine the appropriate mass of the molecule.

[0899] The samples are analyzed on LC-MS with a flow rate of 1mL/min. Solvent A is 15 mM ammonia and solvent B is acetonitrile. The sample is run under positive ion spray on an XBridge C18 3.5 µM (2.1 x 30mm) column, from Waters. The solvent gradient has a total run time of 2 min and ranges from 5% B to 95% B.

[0900] Peak area from the compound in the buffer chamber and the plasma chamber are considered to be 100% compound. The percentage bound to plasma is derived from these results and is reported as percentage bound to plasma.

[0901] The solubility of the compound in the final test concentration in PBS is inspected by microscope to indicate whether precipitation is observed or not.

7.4. Aldehyde oxidase stability

[0902] Aldehyde oxidase is a metabolizing enzyme contained within the cytosolic compartment of many tissues, and is linked to clearance and exposure of a compound. Aldehyde oxidase metabolism may therefore result in reduced efficacy of a compound (Pryde et al., 2010).

[0903] A 10 mM stock solution of test compound in DMSO is first diluted with water (5 fold) to obtain a 50 µM working solution. A selective inhibitor of aldehyde oxidase (hydralazine) is prepared in water as 5 mM solution.

[0904] Incubation mixtures are prepared by adding 10 µL of liver S9 suspension (human and rat, BD Bioscience Gentest, 20 mg/mL) to 86 µL of 50 mM potassium phosphate buffer, pH 7.4 at 37°C. 2 µL of 5 mM hydralazine is added (for incubation with the addition of selective inhibitor) or 2 µL of water (for incubation without the addition of the inhibitor).

[0905] After 5 min pre-warming, the reaction is initiated by the addition of 2 µL of 50 µM test compound to the incubation mixtures. After 0, 3, 6, 12, 18, and 30 min of incubation, the reaction (100 µL) is terminated with 300 µL of MeCN : MeOH (2:1) with 1% acetic acid mixture containing 10 ng/mL of warfarin as analytical internal standard.

[0906] Samples are mixed, centrifuged, and the supernatant analysed by LC-MS.

[0907] Test compounds are considered as a substrate of aldehyde oxidase if clearance by S9 is inhibited by hydralazine. Species specific clearance of test compound may also indicate metabolism by aldehyde oxidase. Phtalazine is included as a positive control.

[0908] The instrument responses (peak area ratio of test compound and internal standard) are referenced to the zero time-point samples (considered as 100%) in order to determine the percentage of compound remaining. Plots of the percentage of test compounds remaining are used to determine the half-life ($T_{1/2}$) and intrinsic clearance in the S9 incubations using Graph Pad Prism software.

[0909] To calculate the in vitro intrinsic clearance (CLint (µL/min/mg), the following formula is used:

[0910] $$CLint = \frac{0.693}{T1/2} * \frac{incubation\ volume}{protein\ amount} * 1000$$

[0911] As illustrated by the table above, when subjected to aldehyde oxidase, in particular in human aldehyde oxidase, the compounds of the invention unexpectedly show an improved profile compared to closely related analogues.

7.5. Liver microsomal stability

[0912] A 10mM stock solution of compound in DMSO is diluted to 6µM in a 105mM phosphate buffer, pH 7.4 in a 96 deep well plate (Greiner, Cat no.780285) and pre-warmed at 37°C.

[0913] A Glucose-6-phosphate-dehydrogenase (G6PDH, Roche, 10127671001) working stock solution of 700U/mL is diluted with a factor 1:700 in a 105mM phosphate buffer, pH7.4. A co-factor mix containing 0.528M $MgCl_2.6H_2O$ (Sigma, M2670), 0.528M glucose-6-phosphate (Sigma, G-7879) and 0.208M NADP+ (Sigma,N-0505) is diluted with a factor 1:8in a 105mM phosphate buffer, pH7.4.

[0914] A working solution is made containing 1 mg/mL liver microsomes (Xenotech) of the species of interest (human, mouse, rat, dog …), 0.8U/mL G6PDH and co-factor mix (6.6mM $MgCl_2$, 6.6 mM glucose-6-phosphate, 2.6mM NADP+). This mix is pre-incubated for 15 min, but never more than 20 min, at room temperature.

[0915] After pre-incubation, compound dilution and the mix containing the microsomes, are added together in equal amount and incubated for 30 min at 300 rpm. For the time point of 0 min, two volumes of MeOH are added to the compound dilution before the microsome mix is added. The final concentration during incubation are: 3µM test compound or control compound, 0.5 mg/mL microsomes, 0.4U/mL G6PDH, 3.3mM $MgCl_2$, 3.3mM glucose-6-phosphate and 1.3mM NaDP+.

[0916] After 30 min of incubation, the reaction is stopped with 2 volumes of MeOH.

[0917] Of both time points, samples are mixed, centrifuged and the supernatant is harvested for analysis on LC-MS/MS. The instrument responses (i.e. peak heights) are referenced to the zero time-point samples (as 100%) in order to determine the percentage of compound remaining. Standard compounds Propanolol and Verapamil are included in the assay design.

[0918] The data on microsomal stability are expressed as a percentage of the total amount of compound remaining after 30 min.

7.6. Hepatocyte stability

[0919] Models to evaluate metabolic clearance in hepatocyte are described by McGinnity et al. Drug Metabolism and Disposition 2008, 32, 11, 1247.

7.7. Caco-2 Permeability

[0920] Bi-directional Caco-2 assays are performed as described below. Caco-2 cells are obtained from European Collection of Cell Cultures (ECACC, cat 86010202) and used after a 21 day cell culture in 24-well Transwell plates (Fisher TKT-545-020B).

[0921] $2x10^5$ cells/well are seeded in plating medium consisting of DMEM + GlutaMAXI + 1% NEAA + 10% FBS (FetalClone II) + 1% Pen/Strep. The medium is changed every 2 – 3 days.

[0922] Test and reference compounds (propranolol and rhodamine123 or vinblastine, all purchased from Sigma) are prepared in Hanks' Balanced Salt Solution containing 25 mM HEPES (pH7.4) and added to either the apical (125µL) or basolateral (600µL) chambers of the Transwell plate assembly at a concentration of 10 µM with a final DMSO concentration of 0.25%.

[0923] 50µM Lucifer Yellow (Sigma) is added to the donor buffer in all wells to assess integrity of the cell layers by monitoring Lucifer Yellow permeation. As Lucifer Yellow (LY) cannot freely permeate lipophilic barriers, a high degree of LY transport indicates poor integrity of the cell layer.

[0924] After a 1 h incubation at 37°C while shaking at an orbital shaker at 150rpm, 70µL aliquots are taken from both apical (A) and basal (B) chambers and added to 100µLl 50:50 acetonitrile:water solution containing analytical internal standard (0.5 µM carbamazepine) in a 96 well plate.

[0925] Lucifer yellow is measured with a Spectramax Gemini XS (Ex 426nm and Em 538nm) in a clean 96 well plate containing 150µL of liquid from basolateral and apical side.

[0926] Concentrations of compound in the samples are measured by high performance liquid-chromatography/mass spectroscopy (LC-MS/MS).

[0927] Apparent permeability (Papp) values are calculated from the relationship:

[0928] P_{app} = $[compound]_{acceptor\ final}$ x $V_{acceptor}$ / ($[compound]_{donor\ initial}$ x V_{donor}) / T_{inc} x V_{donor} / surface area x 60 x 10^{-6} cm/s

V = chamber volume

Tinc = incubation time.

Surface area = 0.33 cm^2

[0929] The Efflux ratios, as an indication of active efflux from the apical cell surface, are calculated using the ratio of P_{app} B>A/ P_{app} A>B.

The following assay acceptance criteria are used:

Propranolol: Papp (A>B) value ≥ 20(x10^{-6} cm/s)

Rhodamine 123 or Vinblastine: Papp (A>B) value < 5 (x10-6 cm/s) with Efflux ratio ≥5.

Lucifer yellow permeability: ≤100 nm/s

7.8. MDCKII-MDR1 Permeability

[0930] MDCKII-MDR1 cells are Madin-Darby canine kidney epithelial cells, over-expressing human multi-drug resistance (MDR1) gene, coding for P-glycoprotein (P-gp). Cells are obtained from Netherlands Cancer Institute and used after a 3-4 day cell culture in 24-well Millicell cell culture insert plates (Millipore, PSRP010R[5]). Bi-directional MDCKII-MDR1 permeability assay is performed as described below.

[0931] 3x105 cells/mL (1.2x105 cells/well) are seeded in plating medium consisting of DMEM + 1% Glutamax-100 + 1% Antibiotic/Antimycotic + 10% FBS (Biowest, S1810). Cells are left in CO_2 incubator for 3-4 days. The medium is changed 24h after seeding and on the day of experiment.

[0932] Test and reference compounds (amprenavir and propranolol) are prepared in Dulbecco's phosphate buffer saline (D-PBS, pH7.4) and added to either the apical (400µL) or basolateral (800µL) chambers of the Millicell cell culture insert plates assembly at a final concentration of 10 µM (0.5 µM in case of amprenavir) with a final DMSO concentration of 1%.

[0933] 100µM Lucifer Yellow (Sigma) is added to the all donor buffer solutions, in order to assess integrity of the cell monolayers by monitoring Lucifer Yellow permeation. Lucifer yellow is a fluorescent marker for the paracellular pathway and it is used as an internal control in every monolayer to verify tight junction integrity during the assay.

[0934] After a 1 h incubation at 37°C while shaking at an orbital shaker at 150rpm, 75µL aliquots are taken from both apical (A) and basal (B) chambers and added to 225µL acetonitrile:water solution (2:1)

containing analytical internal standard (10 ng/mL warfarin) in a 96 well plate. Aliquoting is also performed at the beginning of the experiment from donor solutions to obtain initial (Co) concentration.

[0935] Concentration of compound in the samples is measured by high performance liquid-chromatography/mass spectroscopy (LC-MS/MS).

[0936] Lucifer yellow is measured with a Fluoroscan Ascent FL Thermo Scientific (Ex 485nm and Em 530nm) in a 96 well plate containing 150µL of liquid from all receiver wells (basolateral or apical side).

7.8.1. Ames test

7.8.1.1. Overview

[0937] The purpose of this biological assay is to assess the mutagenic potential of a compound. A positive test indicates that a compound may be carcinogenic, since cancer is often linked to mutation.

[0938] This protocol uses the kit from Moltox (32-102—Ames II™ Mutagenicity Assay Kit by BioReliance™), containing the bacterial strains and growth medium.

7.8.1.2. Material

Reagent	**Reference**
Growth Medium	BioReliance (Sigma Aldrich) 32-26004
TA98 ®	BioReliance (Sigma Aldrich) 32-71098
TAMix®	BioReliance (Sigma Aldrich) 32-71001
Ampicillin	BioReliance (Sigma Aldrich) 32-26007
Exposure Medium	BioReliance (Sigma Aldrich) 32-26002
Reversion Indicator Medium	BioReliance (Sigma Aldrich) 32-26006
S9 SD rat liver Aroclor KCl frozen	Moltox 11-101
Moltox NADPH Regensys “A”	Moltox 60-200.5
Moltox NADPH Regensys “B”	Moltox 60-201.5L
2-Nitrofluorene (2NF)	Sigma-Aldrich N1, 675-4
4-Nitroquinidine 1-oxide (4NQO)	Sigma N8141
2-Aminoanthracene (2AA)	Sigma-Aldrich A3, 880-0

7.8.1.3. Protocol

[0939] Three bacterial cultures are prepared in 50 mL falcon tubes: one blank, one TAMix® and one TA98®. The tip used to pipette the bacteria is left in the tube for good distribution of oxygen during incubation. A sterile cotton wool is used to seal the tube and the bacteria are incubated at 37°C with shaking at 250 rpm overnight.

[0940] The next day the cultures are diluted to 1/10 in growth medium and the OD is measured to check the bacterial growth (blanc = 0, TAmix = 0.2, TA98 = 0.25) and the bacteria are diluted in growth medium to the desired concentration if necessary.

[0941] The test compounds are then dissolved in DMSO at a concentration of 25 mg/mL. If the compound is not soluble at this concentration, more DMSO is added, doubling the final volume, until it is soluble. A serial dilution of the compound up to 0.8 mg/ml is made in a 96 V-bottom polypropylene plate with a dilution factor 2 in DMSO. Control compounds (0.05 mg/mL 4NQO, 0.5mg/mL 2NF and 0.5mg/mL 2AA) are added to the plate as well. 5.1 µL of test compound is transferred to the wells of a 96-deep well masterblock. The final DMSO concentration is 2% and the final compound concentration is at least 500 µg/mL, depending on the primary dilution in DMSO.

[0942] For the incubation with S9, the S9 Moltox mix is prepared by adding 2 mL rat S9 (Moltox 11-101) to 4.66 mL Moltox mix containing reagens A and B (Moltox 60-200.5, Moltox 60-201.5L). The bacteria working solutions are prepared by adding 2 mL of TAMix or TA98 to 18 mL exposure medium or to 15 mL exposure medium and 3 mL S9 Moltox mix.

[0943] From the bacteria working solutions, 250 µL is added to the compound dilutions in the 96 deep-well plates, which are then sealed with an aluminum foil seal and incubated at 37°C for 90 min. After incubation, 1.75 mL of indicator medium is added to all wells. The mixture is transferred to twelve 384 flat bottom plates. The plates are covered with a plastic lid and incubated for 48 h at 37°C in a plastic bag containing a water bowl to avoid evaporation.

[0944] After 48 h incubation, the color of the wells for a genotoxic compound has changed from purple to yellow. Positive wells are checked visually for growth of bacteria. The "fold induction over the negative control" is calculated: the ratio of the mean number of positive wells for the dose concentration divided by the mean number of positive wells for the zero dose (solvent) control. Fold inductions in revertant numbers over the negative control are not considered positive if less than 3. The genotoxicity of compounds is reported as: "> the highest concentration tested that is not toxic (in µg/mL)" or "< the lowest concentration tested", if all concentrations are positive.

7.9. Pharmacokinetic study in rodents

7.9.1. Animals

[0945] Sprague-Dawley rats (male, 5-6 weeks old) are obtained from Janvier (France). Rats are acclimatized for at least 7 days before treatment and are kept on a 12 h light/dark cycle (07h00 – 19h00). Temperature is maintained at approximately 22°C, and food and water are provided ad libitum. Two days before administration of the test compounds, rats underwent surgery to place a catheter in the jugular vein under isoflurane anesthesia. After the surgery, rats are housed individually. Rats are deprived of food for at least 16 h before oral dosing and 6 h after. Water is provided ad libitum.

7.9.2. Pharmacokinetic study

[0946] Compounds are formulated in PEG200/physiological saline (60/40) for the intravenous route and in 0.5% methylcellulose and 10% hydroxylpropyl-β-cyclodextrine pH 3 for the oral route. Test compounds are orally dosed as a single esophageal gavage at 5 mg/kg under a dosing volume of 5 mL/kg and intravenously dosed as a bolus via the caudal vein at 1 mg/kg under a dosing volume of 5 mL/kg. Each group consisted of 3 rats. Blood samples are collected via the jugular vein with lithium heparin as anti-coagulant at the following time points: 0.05, 0.25, 0.5, 1, 3, 5 and 8 h (intravenous route), and 0.25, 0.5, 1, 3, 5, 8 and 24 h (oral route). Alternatively, blood samples are collected at the retro-orbital sinus with lithium heparin as anti-coagulant at the following time points 0.25, 1, 3 and 6 h (oral route). Whole blood samples are centrifuged at 5000 rpm for 10 min and the resulting plasma samples are stored at -20°C pending analysis.

7.9.3. Quantification of compound levels in plasma

[0947] Plasma concentrations of each test compound are determined by an LC-MS/MS method in which the mass spectrometer is operated in positive electrospray mode.

7.9.4. Determination of pharmacokinetic parameters

Pharmacokinetic parameters are calculated using Winnonlin® (Pharsight®, United States).

7.10. 7-Day rat toxicity study

[0948] A 7-day oral toxicity study with test compounds is performed in Sprague-Dawley male rats to assess their toxic potential and toxicokinetics, at daily doses of 100, 300 and 500 mg/kg/day, by gavage, at the constant dosage-volume of 5 mL/kg/day.

[0949] The test compounds are formulated in 30% (v/v) HPβCD in purified water. Each group included 5 principal male rats as well as 3 satellite animals for toxicokinetics. A fourth group is given 30% (v/v) HPβCD in water only, at the same frequency, dosage volume and by the same route of administration, and acted as the vehicle control group.

[0950] The goal of the study is to determine the lowest dose that resulted in no adverse events being identified (no observable adverse effect level - NOAEL).

7.11. Liability for QT prolongation

[0951] Potential for QT prolongation is assessed in the hERG patch clamp assay.

[0952] Whole-cell patch-clamp recordings are performed using an EPC10 amplifier controlled by Pulse v8.77 software (HEKA). Series resistance is typically less than 10 MΩ and compensated by greater than 60%, recordings are not leak subtracted. Electrodes are manufactured from GC150TF pipette glass (Harvard).

[0953] The external bathing solution contained: 135 mM NaCl, 5 mM KCl, 1.8 mM $CaCl_2$, 5 mM Glucose, 10 mM HEPES, pH 7.4.

[0954] The internal patch pipette solution contained: 100mM Kgluconate, 20 mM KCl, 1mM $CaCl_2$, 1 mM $MgCl_2$, 5mM Na_2ATP, 2mM Glutathione, 11 mM EGTA, 10 mM HEPES, pH 7.2.

[0955] Drugs are perfused using a Biologic MEV-9/EVH-9 rapid perfusion system.

[0956] All recordings are performed on HEK293 cells stably expressing hERG channels. Cells are cultured on 12 mm round coverslips (German glass, Bellco) anchored in the recording chamber using two platinum rods (Goodfellow). hERG currents are evoked using an activating pulse to +40 mV for 1000 ms followed by a tail current pulse to –50 mV for 2000 ms, holding potential is -80 mV. Pulses are applied every 20s and all experiments are performed at room temperature.

FINAL REMARKS

[0957] It will be appreciated by those skilled in the art that the foregoing descriptions are exemplary and explanatory in nature, and intended to illustrate the invention and its preferred embodiments. Through routine experimentation, an artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. All such modifications coming within the scope

of the appended claims are intended to be included therein. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

[0958] All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication are specifically and individually indicated to be incorporated by reference herein as though fully set forth.

[0959] It should be understood that factors such as the differential cell penetration capacity of the various compounds can contribute to discrepancies between the activity of the compounds in the *in vitro* biochemical and cellular assays.

[0960] At least some of the chemical names of compound of the invention as given and set forth in this application, may have been generated on an automated basis by use of a commercially available chemical naming software program, and have not been independently verified. Representative programs performing this function include the Lexichem naming tool sold by Open Eye Software, Inc. and the Autonom Software tool sold by MDL, Inc. In the instance where the indicated chemical name and the depicted structure differ, the depicted structure will control.

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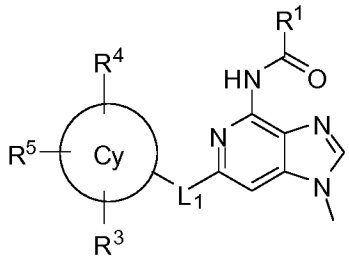
CLAIMS

1) A compound according to Formula I:



I

wherein

R^1 is

– C_{3-4} cycloalkyl, optionally substituted with one or more independently selected C_{1-4} alkyl, halo, or -CN,

– $-CH_3$, $-CH_2-OH$, $-CH_2-CN$, $-CH_2-CH_2-CN$, or

– $-OCH_3$;

L_1 is $-NR^2-$; or -O-;

Cy is

– phenyl, or

– 6 membered heteroaryl comprising 1, 2, or 3 nitrogen heteroatoms;

R^2 is

– H,

– C_{1-4} alkyl optionally substituted with one or more OH,

– C_{2-4} alkenyl comprising on double bond;

R^3 is

– H,

– halo,

– C_{1-4} alkyl optionally substituted with one or more halo, or

– C_{1-4} alkoxy optionally substituted with one or more halo;

R^4 is H, or halo or C_{1-4} alkyl;

R^5 is halo, -CN, or $–L_2-R^6$, wherein

L_2 is

– a bond,

– -W-, or

– $-C_{1-2}$ alkylene-W-;

W is -S-, -O-, $-NR^7-$, -C(=O)-, -C(=O)O-, $-C(=O)NR^7-$, $-NR^7C(=O)-$, $-SO_2-$, $-SO_2NR^7-$, or $-NR^7SO_2-$;

R^6 is

– H,

– C_{1-6} alkyl optionally substituted with one or more independently selected R^8 groups,

– C_{3-7} cycloalkyl, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkyl comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– 4-7 membered heterocycloalkenyl comprising 1 double bond, and comprising 1 or 2 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9,

– C_{6-10} aryl optionally substituted with one or more groups independently selected from R^9, or

– 5-6 membered heteroaryl comprising 1, 2, or 3 heteroatoms independently selected from N, O, and S, optionally substituted with one or more groups independently selected from R^9;

or when is R^5 is $–L_2-R^6$, R^5 and R^2, together may form a fused 6 membered heterocycloalkyl ring with Cy;

R^7 is H, or C_{1-4} alkyl;

R^8 is

– -OH,

– -CN,

– halo, or

– C_{1-4} alkoxy; and

each R^9 is independently selected from

– oxo,

– halo,

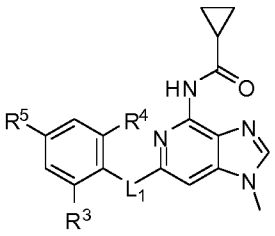
– -CN,

– C_{1-4} alkyl, and

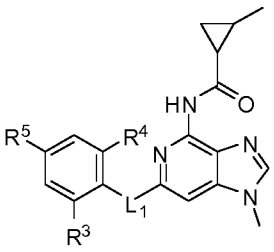
– $-SO_2-C_{1-4}$ alkyl, which alkyl is optionally substituted with one or more halo; or

a pharmaceutically acceptable salt, or a solvate, or the salt of a pharmaceutically acceptable salt thereof.

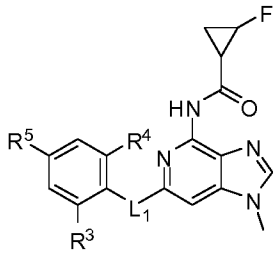
2) A compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula IVa, IVb, IVc, or IVd:



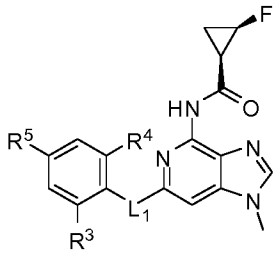
IVa,



IVb,

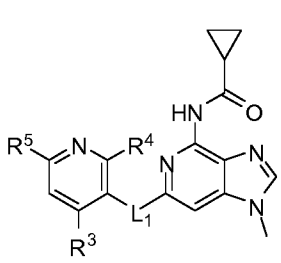


IVc, or

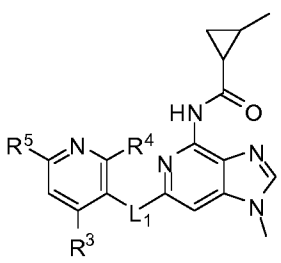


IVd

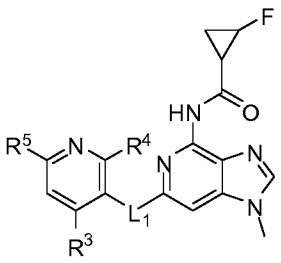
3) A compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula IVa, IVb, IVc, or IVd:



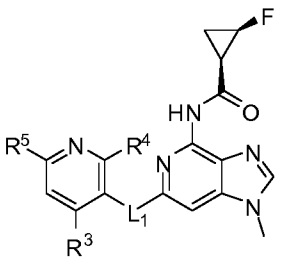
IVi,



IVj,



IVk, or



IVl

4) A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein R^3 is halo.

5) A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein R^3 is C_{1-4} alkyl.

6) A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-3, wherein R^3 is C_{1-4} alkoxy substituted with one or more halo.

7) A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-6, wherein R^4 is halo or C_{1-4} alkyl.

8) A compound or pharmaceutically acceptable salt thereof according to any one of claims 1-7, wherein R^5 is –CN.

9) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein L_1 is –O-.

10) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-8, wherein L_1 is $–NR^2-$.

11) A compound or pharmaceutically acceptable salt thereof, according to claim 10, wherein R^2 is C_{1-4} alkyl.

12) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-11.

13) A pharmaceutical composition, according to claim 12, comprising a further therapeutic agent.

14) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or a pharmaceutical composition according to claim 12 or 13, for use in medicine.

15) A compound or pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or a pharmaceutical composition according to claim 12 or 13, for use in the prophylaxis and/or treatment of diseases involving allergic or inflammatory conditions, autoimmune diseases, proliferative diseases, transplantation rejection, diseases involving impairment of cartilage turnover, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 and/or interferons.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/066520

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61P29/00 A61P37/08 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/117645 A1 (GALAPAGOS NV [BE]) 15 August 2013 (2013-08-15) paragraph [0016] - paragraph [0017] claim 1	1-15
A	WO 2015/006492 A1 (DANA FARBER CANCER INST INC [US]) 15 January 2015 (2015-01-15) page 2, line 18 - line 24 claim 1	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2015	13/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Koch, Kristian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/066520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013117645 A1	15-08-2013	AR 089959 A1	01-10-2014
		AR 089960 A1	01-10-2014
		TW 201336844 A	16-09-2013
		TW 201336845 A	16-09-2013
		US 2013217664 A1	22-08-2013
		US 2013217722 A1	22-08-2013
		UY 34615 A	30-09-2013
		UY 34616 A	30-09-2013
		WO 2013117645 A1	15-08-2013
		WO 2013117646 A1	15-08-2013
WO 2015006492 A1	15-01-2015	NONE	