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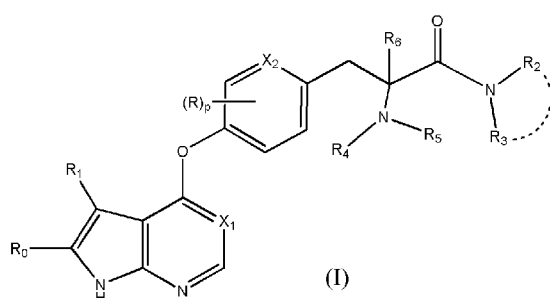
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(54) Title: TYROSINE AMIDE DERIVATIVES AS RHO- KINASE INHIBITORS



(I)

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



TYROSINE AMIDE DERIVATIVES AS RHO- KINASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to compounds inhibiting Rho Kinase (hereinafter ROCK Inhibitors); particularly the invention relates to compounds that are tyrosine amide derivatives, methods of preparing such compounds, pharmaceutical compositions
5 containing them and therapeutic use thereof.

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

Therefore, the compounds of the invention may be useful in the treatment of many
10 disorders associated with ROCK enzymes mechanisms, such as pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

BACKGROUND OF THE INVENTION

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

Both ROCK-II and ROCK-I are expressed in many human and rodent tissues including the heart, pancreas, lung, liver, skeletal muscle, kidney and brain (Riento and Ridley, 2003). ROCK has been identified as an effector molecule of RhoA , and is involved in a variety of cell functions, including actin organization, cell adhesion, cell migration and
25 cytokinesis (Riento and Ridley, 2003; Feng Y, LoGrasso PV, Defert O, Li R. Rho Kinase (ROCK) Inhibitors and Their Therapeutic Potential. J Med Chem. 2016; 59(6):2269-300).

It is also involved in regulating smooth muscle contraction, through the phosphorylation of effectors such as myosin light chain phosphatase (MLC). Indeed ROCK plays an important role in signal transduction initiated by several agents regulating smooth muscle cell contraction in blood vessels and/or airways, including serotonin, angiotensin II, endothelin I, platelet derived growth factor (PDGF) and urotensin II (Li Q, Xu Y, Li X, Guo Y, Liu G. Inhibition of Rho-kinase ameliorates myocardial remodeling and fibrosis in pressure overload and myocardial infarction: role of TGF- β 1-TAK1. *Toxicol Lett.* 2012; 211(2):91-7; Shi J, Wei L. Rho kinases in cardiovascular physiology and pathophysiology: the effect of fasudil. *J Cardiovasc Pharmacol.* 2013; 62(4):341-54). To date only two ROCK inhibitors have been approved for clinical use, in Japan and/or in China: Fasudil (Suzuki Y, Shibuya M, Satoh S, Sugiyama H, Seto M, Takakura K. Safety and efficacy of fasudil monotherapy and fasudil-ozagrel combination therapy in patients with subarachnoid hemorrhage: sub-analysis of the post-marketing surveillance study. *Neurol Med Chir (Tokyo).* 2008; 48(6):241-7) was approved in 1995 for the treatment of cerebral vasospasm, and ripasudil (Tanihara H, Inoue T, Yamamoto T, Kuwayama Y, Abe H, Fukushima A, Suganami H, Araie M; K-115 Clinical Study Group. One-year clinical evaluation of 0.4% ripasudil (K-115) in patients with open-angle glaucoma and ocular hypertension. *Acta Ophthalmol.* 2016; 94(1):e26-34) was approved in 2014 for the treatment of glaucoma.

ROCK mediate vasoconstriction and endothelial dysfunction, two key components of several cardiovascular diseases, including, hypertensive heart disease, coronary artery diseases, atherosclerosis, restenosis, Raynaud phenomenon, stroke and glaucoma (Hartmann S, Ridley AJ, Lutz S. The Function of Rho-Associated Kinases ROCK1 and ROCK2 in the Pathogenesis of Cardiovascular Disease. *Front Pharmacol.* 2015 Nov 20;6:276). In particular, pharmacological data from clinical trials show that ROCK inhibitors decrease intraocular pressure and demonstrate beneficial effects in glaucoma patients (Inoue T, Tanihara H. Rho-associated kinase inhibitors: a novel glaucoma therapy. *Prog Retin Eye Res.* 2013; 37:1-12). In patients with pulmonary hypertension, ROCK activity is significantly higher in both lung tissues and circulating neutrophils as compared

with controls (Duong-Quy S, Bei Y, Liu Z, Dinh-Xuan AT. Role of Rho-kinase and its inhibitors in pulmonary hypertension. *Pharmacol Ther.* 2013;137(3):352-64). A significant correlation was established between neutrophil ROCK activity and the severity and duration of pulmonary hypertension (Duong-Quy et al., 2013). ROCK can also contribute to the development of cardiac fibrosis, hypertrophy, and subsequent heart failure. Recent experimental studies using ROCK inhibitors, such as fasudil, have shown the benefits of ROCK inhibition in cardiac remodeling (Li et al., 2012). Mice lacking each ROCK isoform also exhibit reduced myocardial fibrosis in a variety of pathological models of cardiac remodeling (Shimizu T1, Liao JK. Rho Kinases and Cardiac Remodeling. *Circ J.* 2016; 80(7):1491-8).

ROCK is also a promising target for the treatment of cerebral vascular disorders. Indeed, preclinical studies indicate that Rho kinase inhibition may reduce the formation/growth/rupture of both intracranial aneurysms and cerebral cavernous malformations (Bond LM, Sellers JR, McKerracher L. Rho kinase as a target for cerebral vascular disorders. *Future Med Chem.* 2015;7(8):1039-53).

RhoA-ROCK signalling is important in maintaining a flaccid penile state, and pharmacological inhibition of ROCK signalling potentiates smooth-muscle relaxation in an NO-independent manner, suggesting that ROCK is a new therapeutic target for the treatment of erectile dysfunction (Sopko NA, Hannan JL, Bivalacqua TJ. Understanding and targeting the Rho kinase pathway in erectile dysfunction. *Nat Rev Urol.* 2014;11(11):622-8).

ROCK activity is an important signaling mechanism in leucocyte-platelet-endothelium interaction, leucocyte extravasation and oedema. Overactivation of Rho kinase in endothelial cells causes leakiness by disruption of cell-cell junctions favouring inflammatory cell recruitment. Taken together, this evidence point toward a role of ROCK in pathological conditions associated with acute and chronic inflammation as well as autoimmune diseases. In particular, contribution of the ROCK pathway to autoimmunity and autoimmune disease is emerging (Zanin-Zhorov A, Flynn R, Waksal SD, Blazar BR.

- Isoform-specific targeting of ROCK proteins in immune cells. *Small GTPases*. 2016; 7(3):173-177). This is supported by the demonstration of the role of ROCK signaling in T-cell development and function, including adhesion, chemotactic responses, and antigen-dependent activation, as well as the beneficial effect of ROCK inhibition in experimental models of rheumatoid arthritis and lupus (LoGrasso, P.; Feng, Y. *Rho kinase inhibitors and their application to inflammatory disorders*. *Curr. Top. Med. Chem.* 2009; 9, 704–723; Yoshimi, E.; Kumakura, F.; Hatori, C.; Hamachi, E.; Iwashita, A.; Ishii, N.; Terasawa, T.; Shimizu, Y.; Takeshita, N. Antinociceptive effects of AS1892802, a novel rho kinase inhibitor, in rat models of inflammatory and noninflammatory arthritis. *J. Pharmacol. Exp. Ther.* 2010, 334, 955–963; Stirzaker RA, Biswas PS, Gupta S, Song L, Bhagat G, Pernis AB. Administration of fasudil, a ROCK inhibitor, attenuates disease in lupus-prone NZB/W F1 female mice. *Lupus*. 2012 May;21(6):656-61). The inhibitory effect of Fasudil on T-cell migration might expand its clinical application as a new therapy for multiple sclerosis (Yu JZ, Ding J, Ma CG, Sun CH, Sun YF, Lu CZ, Xiao BG. Therapeutic potential of experimental autoimmune encephalomyelitis by Fasudil, a Rho kinase inhibitor. *J Neurosci Res.* 2010; 88(8):1664-72). Accumulating evidence also demonstrates that ROCK plays a key role in regulating three essential factors for pathogenesis of inflammatory bowel disease (IBD): disruptions of the intestinal barrier, exposure of the luminal content to mucosal immune cells and an abnormal immune response (Huang Y, Xiao S, and Jiang Q. Role of Rho kinase signal pathway in inflammatory bowel disease *Int J Clin Exp Med.* 2015; 8(3): 3089–3097). The clinical use of ROCK inhibitors is under scrutiny also in psoriasis (Yiu ZZ, Warren RB. Novel Oral Therapies for Psoriasis and Psoriatic Arthritis. *Am J Clin Dermatol.* 2016; 17(3):191-200).

There are several lines of evidence that ROCKs play a role in the pathology of diabetes. Indeed, ROCK1 KO mice exhibit insulin resistance and can have a significant increase in glucose-induced insulin secretion, leading to hyperinsulinemia (Lee D. H., Shi J., Jeoung N. H., Kim M. S., Zabolotny J. M., Lee S. W., et al. Targeted disruption of ROCK1 causes insulin resistance in vivo. *J. Biol. Chem.* 2009; 284, 11776–11780). In

addition, studies in models of type 1 and type 2 diabetes have indicated blood pressure-independent nephroprotective actions of ROCKi in diabetic kidney disease (Komers R. Rho kinase inhibition in diabetic kidney disease. *Br J Clin Pharmacol.* 2013;76(4):551-9).

There is now substantial evidence that ROCK is involved in many of the pathways
5 that contribute to the pathologies associated with several acute and chronic pulmonary diseases, including asthma, COPD, bronchiectasis and ARDS/ALI. Given the biological effect of ROCK, selective inhibitors have the potential to treat a number of pathological mechanisms in respiratory diseases, such as smooth muscle hyper-reactivity, bronchoconstriction, airway inflammation and airway remodeling, neuromodulation and
10 exacerbations due to respiratory tract viral infection (Fernandes LB, Henry PJ, Goldie RG. Rho kinase as a therapeutic target in the treatment of asthma and chronic obstructive pulmonary disease. *Ther Adv Respir Dis.* 2007 Oct;1(1):25-33). Indeed the Rho kinase inhibitor Y-27632 causes bronchodilatation and reduces pulmonary eosinophilia trafficking and airways hyperresponsiveness (Gosens, R.; Schaafsma, D.; Nelemans, S. A.; Halayko, A. J. Rhokinase as a drug target for the treatment of airway hyperresponsiveness in asthma. *Mini-Rev. Med. Chem.* 2006, 6, 339–348). Pulmonary ROCK activation has been demonstrated in humans with idiopathic pulmonary fibrosis (IPF) and in animal models of this disease. ROCK inhibitors can prevent fibrosis in these models, and more importantly, induce the regression of already established fibrosis, thus indicating ROCK inhibitors as
15 potential powerful pharmacological agents to halt progression of pulmonary fibrosis (Jiang, C.; Huang, H.; Liu, J.; Wang, Y.; Lu, Z.; Xu, Z. Fasudil, a rho-kinase inhibitor, attenuates bleomycin-induced pulmonary fibrosis in mice. *Int. J. Mol. Sci.* 2012, 13, 8293–8307).

Accumulating evidence supports the concept that ROCK plays important roles in tumor development and progression through regulating many key cellular functions
25 associated with malignancy, including tumorigenicity, tumor growth, metastasis, angiogenesis, tumor cell apoptosis/survival and chemoresistance (Wei L, Surma M, Shi S, Lambert-Cheatham N, Shi J. Novel Insights into the Roles of Rho Kinase in Cancer. *Arch Immunol Ther Exp (Warsz).* 2016; 64(4):259-78). Thus, indicating ROCK inhibitors also

as potential powerful pharmacological agents in cancer.

The administration of an oral ROCK inhibitor effectively ameliorates clinical manifestations in experimental models of graft-vs.-host disease (GVHD). (Biol Blood Marrow Transplant. 2014; 20(8):1104-11; Blood. 2016;127(17):2144-54). Further findings highlight the Rho kinases as rational therapeutic targets to combat tau accumulation in Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD). (Gentry et al., J Neurosci. 2016; 36(4):1316-23)

In various disorders of the central nervous system there is an abnormal activation of the Rho/ROCK pathway. ROCK is activated upon injury to the adult brain and spinal cord and inhibition of ROCKs results in accelerated regeneration and enhanced functional recovery after spinal-cord injury (Kubo T, Hata K, Yamaguchi A, Yamashita T. Rho-ROCK inhibitors as emerging strategies to promote nerve regeneration. Curr Pharm Des. 2007;13(24):2493-9). Inhibition of the Rho/ROCK pathway has also proved to be efficacious in animal models of stroke, inflammatory and demyelinating diseases, Alzheimer's disease and neuropathic pain (reviewed by Mueller, B. K.; Mack, H.; Teusch, N. Rho kinase, a promising drug target for neurological disorders. Nat. Rev. Drug Discovery 2005,4, 387–398).

Various compounds have been described in the literature as Rho Kinase Inhibitors. See e.g. WO2004/039796; WO2006/009889; WO2010/032875; WO2009/079008; WO2014/118133.

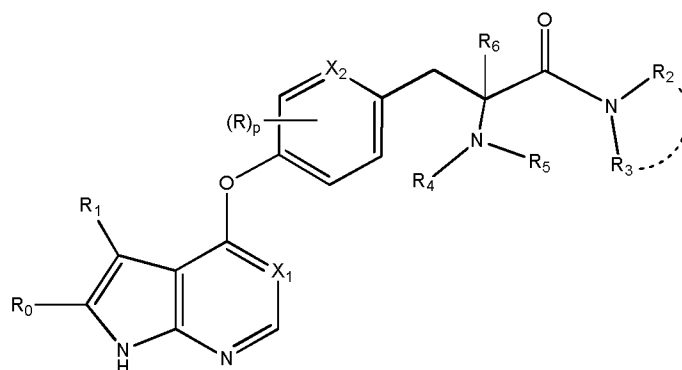
There remains a potential for developing novel and pharmacologically improved ROCK inhibitors in many therapeutic areas such as: cardiovascular and respiratory diseases, erectile dysfunction, fibrotic diseases, insulin resistance, kidney failure, central nervous system disorders, auto-immune diseases and oncology.

In view of the number of pathological responses which are mediated by ROCK enzymes, there is a continuing need for inhibitors of such enzymes which can be useful in the treatment of many disorders. The present invention relates to novel compounds which are inhibitors of ROCK-I and ROCK-II isoforms of the Rho-associated coiled-coil forming

protein kinase (ROCK) that have therapeutically desirable characteristics, particularly promising for some pulmonary diseases including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH) and specifically pulmonary arterial hypertension (PAH).

5 SUMMARY OF THE INVENTION

The present invention is directed to compounds of formula (I)



(I)

10 wherein X₁, X₂, R, R₀, R₁, R₂, R₃, R₄, R₅, R₆ and p are as reported below in the detailed description of the invention, acting as ROCK inhibitors, to processes for the preparation thereof, pharmaceutical compositions comprising them either alone or in combination with one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier.

15 In one aspect the present invention provides the use of a compound of the invention for the manufacture of a medicament.

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

Moreover the present invention provides a method for prevention and/or treatment of any disease wherein a ROCK enzyme inhibition is desirable, said method comprises

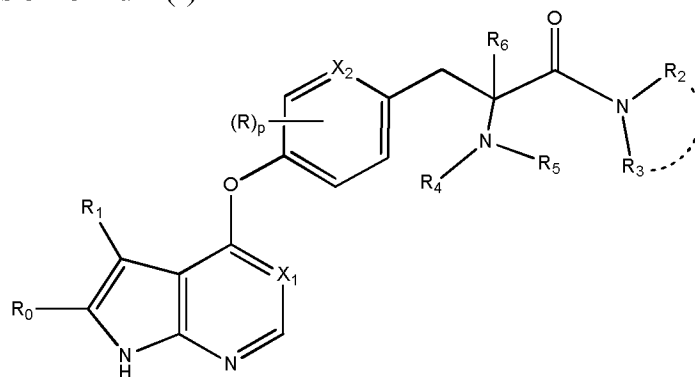
administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention.

In particular the compounds of the invention alone or combined with other active ingredients may be administered for the prevention and/or treatment of a pulmonary disease including asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and pulmonary hypertension (PH) and specifically pulmonary arterial hypertension (PAH).

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to a class of compounds acting as inhibitors of the Rho Kinase (ROCK).

Said class of compounds inhibits the activity or function of the ROCK enzyme and more specifically, they are inhibitors of ROCK-I and ROCK-II isoforms of the Rho-associated coiled-coil forming protein kinase (ROCK). The present invention relates to compounds of formula (I)



(I)

wherein

X_1 , and X_2 are in each occurrence independently a CH group or a nitrogen atom.

p is zero or an integer from 1 to 3;

each R , when present, is a halogen;

R_0 and R_1 are independently selected from the group consisting of

-H,

halogen,

- NR₇R₈,
 -CN,
 (C₁-C₆) alkyl,
 (C₁-C₆) haloalkyl,
 5 (C₁-C₆) hydroxyalkyl,
 (C₁-C₆) aminoalkyl,
 (C₁-C₆) alkoxy-(C₁-C₆) alkyl
 (C₃-C₁₀) cycloalkyl,
 (C₂-C₆) alkenyl,
 10 (C₅-C₇) cycloalkenyl,
 (C₂-C₆) alkynyl,
 (C₂-C₆) hydroxyalkynyl,
 aryl, heteroaryl and (C₃-C₆) heterocycloalkyl
 each of which aryl, heteroaryl and (C₃-C₆) heterocycloalkyl
 15 being in his turn optionally and independently substituted with one or more groups
 selected from
 halogen,
 -OH,
 -CN,
 20 -NR₇R₈,
 -CH₂NR₇R₈,
 (C₁-C₆) alkyl,
 (C₁-C₆) haloalkyl,
 (C₁-C₆) hydroxyalkyl,
 25 (C₂-C₆) alkenyl,
 (C₂-C₆) alkynyl,
 (C₂-C₆) hydroxyalkynyl;
 R₂ and R₃, the same or different, are selected from the group consisting of

-H,

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

(C₁-C₆) hydroxyalkyl,

5 (C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy (C₁-C₆) alkyl,

(C₃-C₁₀)cycloalkyl,

(C₃-C₈)heterocycloalkyl,

aryl,

10 heteroaryl,

aryl(C₁-C₆)alkyl,

heteroaryl(C₁-C₆)alkyl

(C₃-C₈)cycloalkyl(C₁-C₆)alkyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl

15 Each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is further optionally substituted by one or more groups selected independently from halogen, -CN, -OH, (C₁-C₈)alkyl, (C₁-C₆) haloalkyl, (C₁-C₁₀)alkoxy, aryl, aryl(C₁-C₆)alkyl, carbamoyl, (C₁-C₆) aminoalkyl, (C₁-C₆) hydroxyalkyl; or

R₂ and **R₃**, in the alternative, are taken together with the nitrogen atom they are
 20 linked to, to form a mono- or bi-cyclic saturated or partially saturated heterocyclic radical, preferably a 4 to 6 membered monocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one further heteroatom independently selected from N, S or O and/or may bear an -oxo (=O) substituent group, said heterocyclic radical is further optionally including spiro disubstitution as well as
 25 substitution on two adjacent or vicinal atoms forming an additional 5 to 6 membered cyclic or heterocyclic, saturated, partially saturated or aromatic ring;

said heterocyclic radical being optionally in its turn further substituted with one or more groups selected from the group consisting of

- halogen,
- hydroxyl,
- NR₇R₈,
- CH₂NR₇R₈,
- 5 (C₁-C₆) alkyl,
- (C₁-C₆) haloalkyl,
- (C₁-C₆) hydroxyalkyl,
- (C₂-C₆) alkenyl,
- (C₂-C₆) alkynyl,
- 10 (C₂-C₆) hydroxyalkynyl,
- (C₁-C₆) alkoxy (C₁-C₆) alkyl,
- (C₁-C₆) alkanoyl,
- carbamoyl,
- (C₃-C₆) cycloalkyl-carbonyl,
- 15 (C₃-C₆) heterocycloalkyl-carbonyl,
- aryl(C₁-C₆)alkyl,
- aryl alkanoyl,
- arylsulfonyl,
- heteroaryl(C₁-C₆)alkyl,
- 20 heteroaryl-carbonyl
- heteroaryloxyl,
- (C₃-C₆) cycloalkyl,
- (C₃-C₈)cycloalkyl(C₁-C₆)alkyl
- (C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl,
- 25 aryl and heteroaryl

each of said cycloalkyl, aryl and heteroaryl being further optionally substituted by halogen, (C₁-C₈)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₆)alkylthio, (C₁-C₆)aminoalkyl, (C₁-C₆)aminoalkoxyl, carbamoyl, (C₁-C₆)alkyl-sulfonyl;

R₄ and **R₅** are in each occurrence independently selected in the group consisting of
H,

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

5 (C₁-C₆) hydroxyalkyl,

(C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy,

(C₁-C₆) alkoxy-(C₁-C₆) alkyl,

(C₃-C₆) cycloalkyl-(C₁-C₆) alkyl

10 (C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl,

(C₃-C₆) cycloalkyl-carbonyl

(C₃-C₆) heterocycloalkyl-carbonyl

aryl, heteroaryl and (C₃-C₆) heterocycloalkyl;

wherein any of said (C₃-C₆) cycloalkyl, aryl, heteroaryl and (C₃-C₆)

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

halogen,

-OH,

(C₁-C₆) alkyl;

20 **R₆** is selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl;

R₇ and **R₈** are in each occurrence independently selected in the group

H,

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

25 (C₁-C₆) hydroxyalkyl,

(C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy,

(C₁-C₆) alkoxy-(C₁-C₆) alkyl,

(C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl,
aryl, heteroaryl and (C₃-C₆) heterocycloalkyl;

wherein any of said aryl, heteroaryl and (C₃-C₆) heterocycloalkyl in its turn is optionally and independently substituted with one or more groups selected from

5 halogen,

-OH,

(C₁-C₆) alkyl; or

R₇ and R₈ are taken together with the nitrogen atom they are linked to, to form a 4 to 6 membered heterocyclic radical, wherein at least one further ring carbon atom in the
10 said heterocyclic radical may be replaced by at least one group selected from N, S or O;
said heterocyclic radical can be further optionally substituted by a group selected from

H,

-CN,

halogen,

15 -oxo,

-NR₇R₈

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

(C₁-C₆) hydroxyalkyl,

20 (C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy,

(C₁-C₆) alkoxy-(C₁-C₆) alkyl,

alkanoyl;

and pharmaceutically acceptable salt and solvates thereof

25 DEFINITIONS

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

acid conventionally intended as being pharmaceutically acceptable.

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

5 Cations of inorganic bases which can be suitably used to prepare salts within the invention comprise ions of alkali or alkaline earth metals such as potassium, sodium, calcium or magnesium.

Those obtained by reacting the main compound, functioning as a base, with an inorganic or organic acid to form a salt comprise, for example, salts of hydrochloric acid, 10 hydrobromic acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, acetic acid, oxalic acid, maleic acid, fumaric acid, succinic acid and citric acid.

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

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

The expressions “(C₁-C₆) haloalkyl” refer to the above defined “(C₁-C₆)alkyl” groups wherein one or more hydrogen atoms are replaced by one or more halogen atoms, 20 which can be the same or different from each other.

Examples of said (C₁-C₆) haloalkyl groups may thus include halogenated, poly-halogenated and fully halogenated alkyl groups wherein all of the hydrogen atoms are replaced by halogen atoms, e.g. trifluoromethyl or difluoro methyl groups.

By way of analogy, the terms “(C₁-C₆) hydroxyalkyl” or “(C₁-C₆) aminoalkyl” refer 25 to the above defined “(C₁-C₆) alkyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) or amino group respectively. Nonlimiting examples being respectively hydroxymethyl and aminomethyl and the like.

In the present description, unless otherwise provided, the definition of aminoalkyl

encompasses alkyl groups (i.e. “(C₁-C₆) alkyl” groups) substituted by one or more amino group (NR₇R₈). Thus, an example of aminoalkyl is a mono-aminoalkyl group such as R₇R₈N-(C₁-C₆) alkyl.

With reference to the substituent R₇ and R₈ as above defined and below, it is here
5 further explained that when R₇ and R₈ are taken together with the nitrogen atom they are linked to form a 4 to 6 membered heterocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one heteroatom (e.g. N, S or O) and/or may bear -oxo (=O) substituent groups. It is understood that the said heterocyclic radical might be further optionally substituted on any available points in the
10 ring, namely on a carbon atom, or on any heteroatom available for substitution. Substitution on a carbon atom includes spiro disubstitution as well as substitution on two adjacent carbon atoms, in both cases thus form an additional 5 to 6 membered heterocyclic ring. Thus, Examples of said heterocycle radicals are 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, piperazin-4-yl-2-one, 4-methylpiperazine-1-yl, 4-methylpiperazine-1-yl-2-one, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, and (3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl, 8-methyl-2,8-diazaspiro[4.5]decane-2-yl, 5-methyloctahydropyrrolo[3,4-c]pyrrole-2-yl, 1,1-dioxidothiomorpholin-4-yl.

The term “(C₃-C₁₀) cycloalkyl” likewise “(C₃-C₆) cycloalkyl” refers to saturated
20 cyclic hydrocarbon groups containing the indicated number of ring carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and polycyclic ring systems such as adamantan-yl.

The term “(C₂-C₆) alkenyl” refers to straight or branched carbon chains with one or more double bonds, conjugated or not conjugated, in cis or trans configuration, wherein the
25 number atoms is in the range 2 to 6.

By way of analogy, the terms “(C₅-C₇) cycloalkenyl” refers to cyclic hydrocarbon groups containing from 5 to 7 ring carbon atoms and one or two double bonds.

The term “(C₂-C₆) alkynyl” refers to straight or branched carbon chains with one or

more triple bonds wherein the number atoms is in the range 2 to 6.

The term “(C₂-C₆) hydroxyalkynyl” refers to the above defined “(C₁-C₆) alkynyl” groups wherein one or more hydrogen atoms are replaced by one or more hydroxy (OH) group.

5 The term “(C₂-C₆) aminoalkynyl” refers to the above defined “(C₁-C₆) alkynyl” groups wherein one or more hydrogen atoms are replaced by one or more (-NR₇R₈) groups.

 The expression “aryl” refers to mono, bi- or tri-cyclic carbon ring systems which have 6 to 20, preferably from 6 to 15 ring atoms, wherein at least one ring is aromatic. The expression “heteroaryl” refers to mono-, bi- or tri-cyclic ring systems with 5 to 20,
10 preferably from 5 to 15 ring atoms, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom (e.g. N, S or O).

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

15 Examples of suitable aryl or heteroaryl bicyclic ring systems include naphthalenyl, biphenylenyl, purinyl, pteridinyl, pyrazolopyrimidinyl, benzotriazolyl, benzoimidazole-yl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, benzothiophenyl, benzodioxinyl, dihydrobenzodioxinyl, indenyl, dihydro-indenyl, dihydrobenzo[1,4]dioxinyl, benzothiazole-2-yl, dihydrobenzodioxepinyl, benzooxazinyl radicals and the like.

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

 In an analogous manner, the expressions “arylene” and “heteroarylene” refer to divalent groups, such a phenylene, biphenylene and thienylene. Such groups are also
25 commonly named as “arenediyl” or “heteroarenediyl” groups. For example o-phenylene is also named benzene-1,2-diyl. Thienyl-ene is alternatively named thiophenediyl.

 The derived expression “(C₃-C₆) heterocycloalkyl” refers to saturated or partially unsaturated monocyclic (C₃-C₆) cycloalkyl groups in which at least one ring carbon atom

is replaced by at least one heteroatom (e.g. N, S or O) or may bear an -oxo (=O) substituent group. The said heterocycloalkyl (i.e. heterocyclic radical or group) might be further optionally substituted on the available points in the ring, namely on a carbon atom, or on an heteroatom available for substitution. Substitution on a carbon atom includes spiro
 5 disubstitution as well as substitution on two adjacent carbon atoms, in both cases thus form additional condensed 5 to 6 membered heterocyclic ring. Examples of (C₃-C₆) heterocycloalkyl are represented by: pyrrolidinyl, imidazolidinyl, thiazolidinyl, piperazinyl, piperidinyl, morpholinyl, thiomorpholinyl, dihydro- or tetrahydro-pyridinyl, tetrahydropyranyl, pyranyl, 2H- or 4H-pyranyl, dihydro- or tetrahydrofuranlyl,
 10 dihydroisoxazolyl, pyrrolidin-2-one-yl, dihydropyrrolyl radicals and the like.

Specific examples of said heterocycle radicals are 1-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, piperazin-4-yl-2-one, 4-methylpiperazine-1-yl, 1-methylpiperidin-4-yl, 4-methylpiperazine-1-yl-2-one, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, and (3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl.
 15

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

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

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

25 Likewise “(C₁-C₆)alkyl-sulfonyl” refers to a“(C₁-C₆)alkyl-S(O)₂ group wherein alkyl has the meaning above defined. An Example of (C₁-C₆)alkyl-sulfonyl is methylsulfonyl.

The term “carbamoyl” refers to amino carbonyl derived groups -C(O)N R₇R₈, wherein R₇ and R₈ are as defined above in the definition of aminoalkyl groups and including

substituted (preferred aminoalkyl substituted) and spiro substituted derivatives. Examples of such carbamoyl groups being aminocarbonyl, piperazine-1-carbonyl, morpholine-N-carbonyl, morpholine-N-carbonyl and N-(2-(dimethylamino)ethyl)aminocarbonyl, N-(2-(dimethylamino)ethyl)-N-methylaminocarbonyl, N-(3-(dimethylamino)propyl)-N-methylaminocarbonyl, 4-methylpiperazine-1-carbonyl, 4-(dimethylamino)piperidin-1-carbonyl, N-(2-(4-methylpiperazin-1-yl)ethyl)aminocarbonyl, (2 morpholino-ethyl) aminocarbonyl, N-methyl-N-(2 morpholino-ethyl) aminocarbonyl, N-(2-(piperidin-1-yl)ethyl) aminocarbonyl, N-methyl-N-(2-(piperidin-1-yl)ethyl)aminocarbonyl, N-(1-methylpiperidin-4-yl-methyl) aminocarbonyl, N-methyl-N-(1-methylpiperidin-4-yl)aminocarbonyl, N-methyl-N-(1-methylpiperidin-4-yl)aminocarbonyl, 5-methyloctahydropyrrolo[3,4-c]pyrrole-2 carbonyl.

The term “hydroxycarbonyl” refers to a terminal group HOC(O)-.

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

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

By analogy, derived expressions “(C₃-C₆) heterocycloalkyloxy” and “(C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy” refer to heterocycloalkyl groups attached through an oxygen bridge and chained heterocycloalkyl-alkoxy groups respectively. Examples of such (C₃-C₆) heterocycloalkyloxy and (C₃-C₆) heterocycloalkyl (C₁-C₆) alkoxy groups are respectively (piperidin-4-yl)oxy, 1-methylpiperidin-4-yl)oxy, 2-(piperidin-4-yl)ethoxy, 2-(1-methylpiperidin-4-yl)ethoxy, and 2-(4-morpholino)ethoxy.

The derived expressions “Aryloxy” and “Aryl (C₁-C₆) alkoxy” likewise “heteroAryloxy” and “Heteroaryl (C₁-C₆) alkoxy” refer to Aryl or Heteroaryl groups attached through an oxygen bridge and chained Aryl-alkoxy or HeteroAryl-alkoxy

groups. Examples of such are phenyloxy and benzyloxy and pyridinyloxy respectively.

Likewise derived expression “(C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl” and “(C₃-C₆) cycloalkyl-(C₁-C₆) alkyl” refer to the above defined heterocycloalkyl and cycloalkyl groups attached to the rest of the molecule via an alkyl group of the indicated number of carbons.

5 Examples being piperidin-4-yl-methyl, cyclohexylethyl.

The derived expression “(C₁-C₆) alkoxy-(C₁-C₆) alkyl” refers to the above defined alkoxy group attached to the rest of the molecule via an alkyl group of the indicated number of carbons. Examples being methoxymethyl.

10 The derived expression “(C₁-C₆) alkoxycarbonyl” refers to the above defined alkoxy group attached to the rest of the molecule via a carbonyl group. Examples being ethoxycarbonyl.

Further derived expression like “(C₁-C₆) alkoxycarbonyl-amino” refers to the above defined alkoxy group attached to the rest of the molecule via a carbonyl group followed by an amino group (-NR₇-). An example of (C₁-C₆) alkoxycarbonyl-amino is tert-butoxy-carbonyl-amino-.

Thus, “(C₁-C₆) alkoxycarbonyl (C₃-C₆) heterocycloalkyl (C₁-C₆) alkyl” refers to alkoxy carbonyl heterocycloalkyl substituents enchain in the said order and attached to the rest of the molecule via an alkyl group of the indicated number of carbons. An example is (tert-butyl piperidine-1-carboxylate)-4 yl-methyl.

20 The derived expression “(C₁-C₆) aminoalkoxyl” refers to (C₁-C₆) aminoalkyl groups as above defined attached through an oxygen bridge, for example (2-(dimethylamino)ethoxy).

The expression “(C₁-C₆) hydroxyalkoxyl” refers to hydroxyalkyl groups as above defined attached to the rest of the molecule through an oxygen bridge, for example 25 hydroxyethoxy.

The derived expression “(C₁-C₆) aminoalkylcarbamoyl” refers to a “carbamoyl” group, as above defined, substituted with a (C₁-C₆) aminoalkyl group (i.e. -C(O)NR₇R₈ wherein e.g. R₈ is an (C₁-C₆) aminoalkyl). An example is 2(dimethylamino) ethyl carbamoyl.

The term “aryl alkanoyl” refers to an arylC(O) or arylalkylcarbonyl group [e.g. Aryl(C₁-C₆)alkylC(O)-] wherein aryl and alkyl have the meaning above defined. Examples are represented by benzoyl, phenylacetyl, phenylpropanoyl or phenylbutanoyl radicals. Likewise “aryl sulfonyl” refers to an arylS(O)₂ group wherein aryl has the meaning above defined. An examples is phenylsulfonyl.

Further likewise, enchainned substituents derive their definition from the composing fragments, like in the above provided definitions, such as “(C₃-C₆) cycloalkyl-carbonyl”, “(C₃-C₆) heterocycloalkyl-carbonyl”, “heteroaryl-carbonyl”; referring to the above defined fragments attached to the rest of the molecule via a carbonyl group. Examples of such groups being cyclopropanecarbonyl, pyrrolidine-3-carbonyl, (pyridin-3-yl)carbonyl.

The expression “saturated, partially unsaturated or aromatic, five or six membered cycloalkane-diyl, arylene-diyl or heterocycle-diyl” refers to suitable disubstituted cycloalkane or heterocycle or aromatic residue with five or six elements including 1,2-, 1,3- or 1,4-benzene-diyl; 2,3-, 3,4-, 4,5- or 5,6- pyridine-diyl; 3,4-, 4,5- or 5,6- pyridazine-diyl; 4,5- or 5,6- pyrimidine-diyl; 2,3-pyrazinediyl; 2,3-, 3,4- or 4,5- thiophene-diyl / furane-diyl / pyrrole-diyl; 4,5-imidazole-diyl / oxazole-diyl / thiazole-diyl; 3,4- or 4,5-pyrazole-diyl / isoxazole-diyl / isothiazole-diyl their saturated or partially unsaturated analogues and the like. Other non vicinal disubstituted residues (diradical) are included too, such as 4,6- pyrimidine-diyl and the like.

As used herein, the expression “ring system” refers to mono- or bicyclic or polycyclic ring systems which may be saturated, partially unsaturated or unsaturated, such as aryl, (C₃-C₁₀) cycloalkyl, (C₃-C₆) heterocycloalkyl or heteroaryl.

As used herein the terms “group”, “radical” or “fragment” or “substituent” are synonymous and are intended to indicate functional groups or fragments of molecules attachable to a bond or other fragments or molecules. Thus, as an example, a “heterocyclic radical” herein refers to a mono- or bi-cyclic saturated or partially saturated heterocyclic moiety (group, radical), preferably a 4 to 6 membered monocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least

one further heteroatom independently selected from N, S or O and/or may bear an -oxo (=O) substituent group, said heterocyclic radical is further optionally including spiro disubstitution as well as substitution on two adjacent or vicinal atoms forming an additional 5 to 6 membered cyclic or heterocyclic, saturated, partially saturated or aromatic ring. Thus, examples of said heterocycle radicals are 1-pyrrolidinyl, 1-piperidinyl, 1-piperazinyl, 4-morpholinyl, piperazin-4-yl-2-one, 4-methylpiperazine-1-yl, 4-methylpiperazine-1-yl-2-one, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, and (3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl and the like.

A dash (“-”) that is not between two letters or symbols is meant to represent the point of attachment for a substituent. When graphically represented the point of attachment in a cyclic functional group is indicated with a dot (“•”) localized in one of the available ring atom where the functional group is attachable to a bond or other fragment of molecules.

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

When a numerical index is used like in the statement “p is zero or an integer from 1 to 3” the statement (value) “p is zero” means that the substituent R is absent, that is to say there is no substituent R on the ring.

Whenever basic amino or quaternary ammonium groups are present in the compounds of formula I, physiological acceptable anions, selected among chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, p-toluenesulfonate, pamoate and naphthalene disulfonate may be present. Likewise, in the presence of acidic

groups such as COOH groups, corresponding physiological cation salts may be present as well, for instance including alkaline or alkaline earth metal ions.

It will be apparent to those skilled in the art that compounds of formula (I) when contain one or more stereogenic center, may exist as optical stereoisomers.

5 Where the compounds according to the invention have at least one stereogenic center, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more stereogenic centers, they may additionally exist as diastereoisomers. It is to be understood that all such single enantiomers, diastereoisomers and mixtures thereof in any proportion are encompassed within the scope of the present
10 invention. The absolute configuration (R) or (S) for carbon bearing a stereogenic center is assigned on the basis of Cahn-Ingold-Prelog nomenclature rules based on groups' priorities.

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

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

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

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

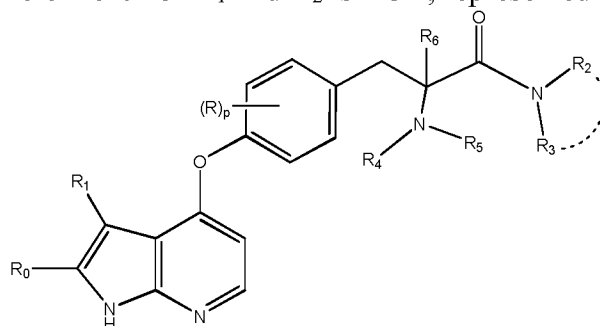
Racemic forms of compounds of formula (I) as well as the individual atropisomers (substantially free of its corresponding enantiomer) and stereoisomer-enriched

atropisomers mixtures are included in the scope of the present invention.

The invention further concerns the corresponding deuterated derivatives of compounds of formula (I).

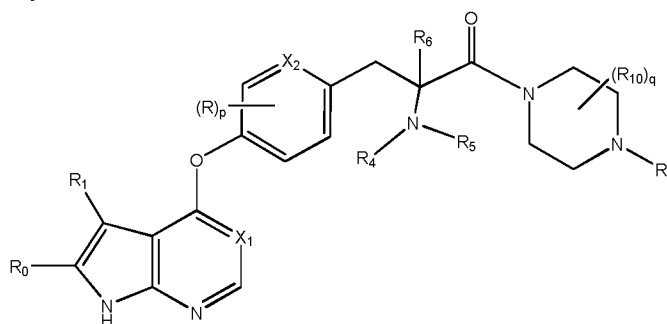
It is to be understood that all preferred groups or embodiments described above and herebelow for compounds of formula I may be combined among each other and apply as well *mutatis mutandis*.

In a preferred embodiment, the invention is directed to compounds of formula (I) as above defined wherein each of X_1 and X_2 is a CH; represented by the formula Ia:



Ia

In a second preferred embodiment, the invention is directed to compounds of formula (I) as above defined wherein **R₂** and **R₃**, are taken together with the nitrogen atom they are linked to, to form a mono-cyclic saturated heterocyclic radical, which is a piperazine ring; represented by the formula Ib:



Ib

wherein **R₉** is selected from the group consisting of

(C₁-C₆) alkyl,

(C₁-C₆) alkoxy(C₁-C₆) alkyl,

(C₁-C₆) alkanoyl,

carbamoyl,

(C₃-C₆) cycloalkyl-carbonyl,

(C₃-C₆) heterocycloalkyl-carbonyl,

aryl(C₁-C₆)alkyl,

5 aryl alkanoyl,

arylsulfonyl,

heteroaryl(C₁-C₆)alkyl,

heteroaryl-carbonyl,

heteroaryloxy,

10 (C₃-C₆) cycloalkyl,

(C₃-C₈)cycloalkyl(C₁-C₆)alkyl

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

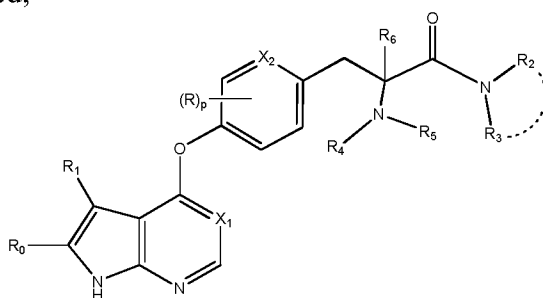
aryl and heteroaryl

each of said cycloalkyl, heterocycloalkyl, aryl and heteroaryl being further
15 optionally substituted by one or more halogen, (C₁-C₈)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₆)alkylthio, (C₁-C₆) aminoalkyl, (C₁-C₆) aminoalkoxy, carbamoyl, (C₁-C₆)alkyl-sulfonyl;

and wherein said piperazine ring is further optionally substituted by one or more
substituent group R₁₀ selected in the group consisting of (C₁-C₆) alkyl, (C₁-C₆)
hydroxyalkyl and aryl;

20 all the other variables being as defined above.

In a third preferred embodiment, the invention is directed to compounds of formula
(I) as above defined,



(I)

wherein

X₁, and **X₂** are both a CH group;

p is zero or an integer from 1 to 3

each **R**, when present, is a halogen;

5 **R₀** is -H and

R₁ is independently selected from the group consisting of

-CN,

(C₁-C₆) alkyl,

(C₁-C₆) hydroxyalkyl,

10 **R₂** is -H,

and **R₃**, is selected from the group consisting of

(C₃-C₁₀)cycloalkyl,

(C₃-C₈)heterocycloalkyl,

heteroaryl(C₁-C₆)alkyl;

15 each of said heteroaryl, cycloalkyl, heterocycloalkyl is further optionally substituted by one or more (C₁-C₈)alkyl or (C₁-C₆) hydroxyalkyl;

R₄ and **R₅** are both H,

R₆ is -H;

and pharmaceutically acceptable salt and solvates thereof.

20 A preferred group of compounds according to the invention are compounds of formula (I)

wherein

X₁, and **X₂** are in each occurrence independently a CH group or a nitrogen atom;

p is zero or an integer from 1 to 3;

25 each **R**, when present, is fluoro;

R₀ is -H or (C₁-C₆) alkyl which is methyl, and **R₁** is independently selected from the group consisting of

-H,

- Halogen which is Bromo, Chloro, Iodo, Fluoro,
 -NR₇R₈,
 -CN,
 (C₁-C₆) alkyl which is methyl,
 5 (C₁-C₆) haloalkyl,
 (C₁-C₆) hydroxyalkyl which is hydroxymethyl, hydroxyethyl,
 (C₁-C₆) aminoalkyl,
 (C₁-C₆) alkoxy-(C₁-C₆) alkyl which is methoxymethyl,
 (C₃-C₁₀) cycloalkyl which is cyclopropyl,
 10 (C₂-C₆) alkenyl,
 (C₅-C₇) cycloalkenyl,
 (C₂-C₆) alkynyl,
 (C₂-C₆) hydroxyalkynyl which is hydroxypropynyl,
 aryl which is phenyl, hydroxyphenyl,
 15 heteroaryl which is isoxazolyl, N-methylimidazolyl, pyridinyl, thiazolyl, N-ethyl
 pyrazolyl, thiophenyl-carbonitrile, and
 (C₃-C₆) heterocycloalkyl which is dihydropyrrolyl, dihydrofuranyl,
R₂ is -H or (C₁-C₆) alkyl which is methyl and R₃, is independently selected from
 the group consisting of
 20 (C₁-C₆) alkyl which is methyl,
 (C₁-C₆) haloalkyl,
 (C₁-C₆) hydroxyalkyl,
 (C₁-C₆) aminoalkyl which is dimethylaminoethyl, dimethylaminopropyl,
 (C₁-C₆) alkoxy (C₁-C₆) alkyl which is methoxypropyl,
 25 (C₃-C₁₀)cycloalkyl which is cyclohexyl, hydroxymethylcyclohexyl,
 hydroxyethylcyclohexyl, cyano-cyclohexyl, 4-aminocarbonyl-cyclohexane-4-yl, 4-
 dimethylaminomethyl-cyclohexane-4-yl,
 (C₃-C₈)heterocycloalkyl which is N-methylpiperidinyl, (hydroxymethyl)-N-

methylpiperidinyl, N-benzylpiperidinyl, N-methylazetidin-3-yl, tetrahydropyranyl, 4-hydroxymethyl-tetrahydropyran-4-yl, quinuclidinyl,

aryl which is phenyl, trifluoromethylphenyl, dihydroindenyl,

heteroaryl which is thiazolyl, pyridinyl, chloropyridinyl, isoquinolinyl,

5 aryl(C₁-C₆)alkyl which is benzyl, o-, m-, p-hydroxymethylbenzyl, phenethyl,

heteroaryl(C₁-C₆)alkyl which is (pyridinyl)ethyl, (thiophene-yl)methyl, (N-phenyl-pyrazolyl)ethyl,

(C₃-C₈)cycloalkyl(C₁-C₆)alkyl which is cyclohexylmethyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl which is (piperidin-4-yl)methyl, (N-benzylpiperidinyl)methyl, (N-methylpiperidin-4-yl)methyl, N-methylazetidin-3-yl-methyl, morpholinopropyl; or

R₂ and **R₃**, in the alternative, taken together with the nitrogen atom they are linked to, form a mono-cyclic group which is piperazin-N-yl, methylpiperazin-N-yl, phenyl-N-methylpiperazin-N-yl, N-phenyl-piperazin-N-yl, trimethylpiperazin-N-yl, 4-benzyl-3,5-dimethylpiperazin-N-yl, (hydroxymethyl)-N-methylpiperazin-N-yl, acetyl(piperazin-N-yl), phenylacetyl(piperazin-N-yl), benzoyl(piperazin-N-yl), 4-(((dimethylamino)methyl)benzoyl)piperazin-1-yl, cyclopropyl(piperazin-N-yl), cyclopropylmethyl(piperazin-N-yl), cyclopropanecarbonyl(piperazin-N-yl), cyclohexanecarbonyl(piperazin-N-yl), N-methylpiperidine-4-carbonyl(piperazin-N-yl), 4-(pyridine-3-carbonyl)piperazin-N-yl, 4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-N-yl, 4-(1-methyl-1H-imidazole-4-carbonyl)piperazin-N-yl, 4-(1H-thiazole-4-carbonyl)piperazin-N-yl, 4-dimethylaminocarbonyl(piperazin-N-yl), (phenylsulfonyl)piperazin-N-yl, (pyridinyl)piperazin-N-yl, (pyridinylmethyl)piperazin-N-yl, (methoxyethyl)piperazin-N-yl, (benzyl)piperazin-N-yl, (methoxybenzyl)piperazin-N-yl, (3-(dimethylaminopropoxy)benzyl)piperazin-N-yl, (fluorobenzyl)piperazin-N-yl, (methylbenzyl)piperazin-N-yl, N-(((methylaminocarbonyl)phenyl)methyl)piperazine-N-yl, N-(((methylaminocarbonyl)furanyl)methyl)piperazine-N-yl, (phenethyl)piperazin-N-yl, (pyrimidinylmethyl)piperazin-N-yl, (2(methylthio)pyrimidinylmethyl)piperazin-N-yl,

(((methylsulfonyl)piperidin-4-yl)methyl)piperazin-N-yl, ((N-methyl-imidazol-5-yl)methyl)piperazin-N-yl, ((1-methyl-1H-imidazol-2-yl)methyl)piperazin-N-yl, ((methylthiazolyl)methyl)piperazin-N-yl, ((pyrazin-2-yl)methyl)piperazin-N-yl, ((1-methyl-1H-pyrazol-4-yl)methyl)piperazin-N-yl, benzo[d][1,3]dioxol-5-ylmethyl)piperazin-N-yl, (quinoxalin-2-ylmethyl)piperazin-N-yl, ((1,2,3-thiadiazol-4-yl)methyl)piperazin-N-yl, (pyridazin-4-ylmethyl)piperazin-N-yl, pyrrolidin-N-yl, phenylpyrrolidin-N-yl, (pyridinyl)pyrrolidin-N-yl, piperidin-N-yl, (dimethylamino)piperidin-N-yl, 4-((dimethylamino)methyl)piperidin-N-yl, benzylpiperidin-N-yl, benzylhydroxypiperidin-N-yl, pyridinylpiperidin-N-yl, pyridinyloxypiperidin-N-yl, (phenylsulfonyl)piperidin-N-yl, 4-phenyl-5,6-dihydropyridin-1(2H)-yl, phenylmorpholin-N-yl, 3-(dimethylamino)azetidin-N-yl, 3-(dimethylamino)methyl-azetidin-N-yl, 3-(dimethylamino)pyrrolidin-N-yl, 3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-N-yl, 3-(dimethylamino)piperidin-N-yl, or a bi-cyclic group which is 5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl, 3,4-dihydro-2,7-naphthyridin-2(1H)-yl, 1H-pyrrolo[3,4-c]pyridin-2(3H)-yl, hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl, 3,4-dihydroisoquinolin-2(1H)-yl, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl, octahydropyrrolo[3,4-c]pyrrol-2-yl or 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl;

R₄ is selected in the group consisting of H, (C₁-C₆) alkyl which is methyl, (C₃-C₆) cycloalkyl-(C₁-C₆) which is cyclohexylmethyl, and (C₃-C₆) cycloalkyl-carbonyl which is cyclohexylcarbonyl or (pyrrolidin-3-yl)carbonyl;

and **R₅** is independently selected in the group consisting of H, (C₁-C₆) alkyl which

is methyl;

R₆ is selected from the group consisting of -H, and (C₁-C₆) alkyl which is methyl; and pharmaceutically acceptable salt and solvates thereof.

The invention also provides a pharmaceutical composition comprising a compound
5 of formula I, or a pharmaceutically acceptable salt thereof in admixture with one or more pharmaceutically acceptable carrier or excipient, either alone or in combination with one or more further active ingredient.

In one aspect the invention provides a compound of formula (I) for use as a medicament.

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

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

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

In particular the invention provides methods for the prevention and/or treatment wherein the disorder is asthma, chronic obstructive pulmonary disease COPD idiopathic pulmonary fibrosis (IPF), Pulmonary hypertension (PH) and specifically Pulmonary
25 Arterial Hypertension (PAH).

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

Ex. N.	Chemical Name
1	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide
2	(S)-2-amino-1-(7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
3	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one
4	(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylmorpholino)propan-1-one
5	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenylpiperazin-1-yl)propan-1-one
6	(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methyl-3-phenylpiperazin-1-yl)propan-1-one
7	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one
8	(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one
9	(S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
10	(S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
11	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yl)oxy)piperidin-1-yl)propan-1-one
12	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one
13	(S)-2-amino-1-(4-benzylpiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
14	(S)-2-amino-1-(4-(dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
15	(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
16	(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propan-1-one
17	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one
18	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3,3,4-trimethylpiperazin-1-yl)propan-1-one
19	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-methoxyethyl)piperazin-1-yl)propan-1-one
20	(S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
21	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)propan-1-one
22	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperazin-1-yl)propan-1-one
23	(S)-4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)-N,N-dimethylpiperazine-1-carboxamide
24	(S)-2-amino-1-((1S,4S)-5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one

Ex. N.	Chemical Name
25	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one
26	(S)-2-amino-1-((3S,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
27	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one
28	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-ylmethyl)piperazin-1-yl)propan-1-one
29	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one
30	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one
31	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one
32	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(hydroxymethyl)cyclohexyl)propanamide
33	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)propanamide
34	(S)-2-amino-N-(1-cyanocyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
35	(S)-1-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamido)cyclohexanecarboxamide
36	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(2-hydroxyethyl)cyclohexyl)propanamide
37	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)-1-methylpiperidin-4-yl)propanamide
38	(S)-2-amino-N-(1-(dimethylamino)methyl)cyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
39	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-N-((1-methylpiperidin-4-yl)methyl)propanamide
40	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylpiperidin-4-yl)methyl)propanamide
41	(S)-2-amino-1-(3-(dimethylamino)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
42	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylazetidin-3-yl)propanamide
43	(S)-2-amino-1-((R)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one

Ex. N.	Chemical Name
44	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-N-((1-methylpiperidin-4-yl)propanamide
45	(S)-2-amino-1-(4-((dimethylamino)methyl)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
46	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((R)-quinuclidin-3-yl)propanamide
47	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylazetidin-3-yl)methyl)propanamide
48	(S)-2-amino-1-(3-((dimethylamino)methyl)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
49	(S)-2-amino-1-((S)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
50	(S)-2-amino-1-((R)-3-(dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
51	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-ylmethyl)piperazin-1-yl)propan-1-one
52	2-amino-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
53	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenethylpiperazin-1-yl)propan-1-one
54	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
55	(R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
56	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(1-phenyl-1H-pyrazol-4-yl)ethyl)propanamide
57	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide
58	2-amino-1-(4-(cyclopropylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
59	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one
60	2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
61	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(thiophen-2-ylmethyl)propanamide
62	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)benzyl)propanamide
63	2-amino-N-(2,3-dihydro-1H-inden-2-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
64	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-(hydroxymethyl)-4-methylpiperazin-1-yl)propan-1-one
65	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)propan-1-one
66	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(pyridin-4-yl)pyrrolidin-1-yl)propan-1-one
67	2-amino-1-(3,4-dihydro-2,7-naphthyridin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one

Ex. N.	Chemical Name
68	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-methoxypropyl)propanamide
69	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-2-yl)ethyl)propanamide
70	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-3-yl)propanamide
71	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-4-yl)propanamide
72	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methylbenzyl)piperazin-1-yl)propan-1-one
73	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(3-methylbenzyl)piperazin-1-yl)propan-1-one
74	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-fluorobenzyl)piperazin-1-yl)propan-1-one
75	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methoxybenzyl)piperazin-1-yl)propan-1-one
76	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenethylpropanamide
77	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperidin-1-yl)propan-1-one
78	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(isoquinolin-5-yl)propanamide
79	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-morpholinopropyl)propanamide
80	2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)propan-1-one
81	2-amino-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
82	2-amino-N-((1-benzylpiperidin-4-yl)methyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
83	2-amino-N-(1-benzylpiperidin-4-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
84	First eluting rac-diastereoisomer 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one
85	Second eluting rac-diastereoisomer 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one
86	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
87	(S)-2-amino-N-(3-methoxypropyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
88	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
89	(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide
90	(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
91	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide
92	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide
93	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-N-methylpropanamide
94	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(6-chloropyridin-3-yl)propanamide

Ex. N.	Chemical Name
95	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide
96	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide
97	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide
98	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide
99	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide
100	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide
101	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide
102	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide
103	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide
104	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide
105	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide
106	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide
107	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide
108	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide
109	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide
110	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide
111	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide
112	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide
113	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N,N-dimethylpropanamide
114	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
115	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one
116	(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propanamide
117	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide
118	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one
119	(S)-2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one
120	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one
121	2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one
122	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one

Ex. N.	Chemical Name
123	(S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one
124	(S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one
125	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
126	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yl)oxy)piperidin-1-yl)propan-1-one
127	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one
128	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide
129	(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one
130	(S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile
131	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-(methylamino)propanamide
132	2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
133	1-(4-acetyl)piperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
134	(S)-2-amino-N-cyclohexyl-N-methyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
135	(S)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
136	(R)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
137	(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide
138	(R)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide
139	(S)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
140	(R)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
141	(S)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
142	(R)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
143	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide
144	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-N-methylpropanamide
145	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide
146	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-cyclohexylpropanamide
147	(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-phenylpropanamide
148	(R)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
149	(R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide
150	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-2-methylpropanamide
151	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-2-methyl-N-(tetrahydro-2H-pyran-4-yl)propanamide

Ex. N.	Chemical Name
152	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperazin-1-yl)propan-1-one
153	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridazin-4-ylmethyl)piperazin-1-yl)propan-1-one
154	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-(methylthio)pyrimidin-4-yl)methyl)piperazin-1-yl)propan-1-one
155	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)propan-1-one
156	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)propan-1-one
157	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-methylthiazol-4-yl)methyl)piperazin-1-yl)propan-1-one
158	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)propan-1-one
159	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(quinoxalin-2-ylmethyl)piperazin-1-yl)propan-1-one
160	(S)-2-amino-1-(4-(4-(3-(dimethylamino)propoxy)benzyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
161	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)propan-1-one
162	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyrimidin-5-ylmethyl)piperazin-1-yl)propan-1-one
163	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-pyrazol-4-yl)methyl)piperazin-1-yl)propan-1-one
164	(S)-1-(4-((1,2,3-thiadiazol-4-yl)methyl)piperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
165	(S)-3-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)-N-methylbenzamide
166	(S)-5-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)-N-methylfuran-2-carboxamide
167	(S)-2-amino-1-(4-benzoylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one

Ex. N.	Chemical Name
168	(S)-2-amino-1-(4-(cyclohexanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
169	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-phenylacetyl)piperazin-1-yl)propan-1-one
170	(S)-2-amino-1-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
171	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methylpiperidine-4-carbonyl)piperazin-1-yl)propan-1-one
172	(S)-2-amino-1-(4-(4-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
173	(S)-2-amino-1-(4-(3-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
174	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-nicotinoyl)piperazin-1-yl)propan-1-one
175	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)propan-1-one
176	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-imidazole-4-carbonyl)piperazin-1-yl)propan-1-one
177	(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(thiazole-2-carbonyl)piperazin-1-yl)propan-1-one
178	N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(dimethylamino)-1-oxopropan-2-yl)pyrrolidine-3-carboxamide
179	N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-(phenylamino)propan-2-yl)pyrrolidine-3-carboxamide
180	N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)pyrrolidine-3-carboxamide
181	N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((2-(dimethylamino)ethyl)amino)-1-oxopropan-2-yl)cyclohexanecarboxamide
182	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-(dimethylamino)-N-(tetrahydro-2H-pyran-4-yl)propanamide
183	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-(dimethylamino)propanamide
184	(S)-N-cyclohexyl-2-(dimethylamino)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
185	3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-((cyclohexylmethyl)amino)-N-methylpropanamide
186	(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide
187	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)propan-1-one
188	(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide
189	(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide

Ex. N.	Chemical Name
190	(S)-2-amino-N-cyclohexyl-3-(4-((3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
191	(S)-2-amino-3-(4-((3-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide
192	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
193	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-ethyl-1H-pyrazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
194	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
195	(S)-5-(4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)phenoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carbonitrile
196	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
197	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-methyl-1H-imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
198	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(isoxazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
199	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
200	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
201	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydrofuran-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
202	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydro-1H-pyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
203	(S)-2-amino-N-cyclohexyl-3-(4-((3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
204	(S)-2-amino-3-(3-fluoro-4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide
205	(S)-2-amino-3-(3-fluoro-4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide
206	(S)-2-amino-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide
207	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
208	(S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
209	(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
210	(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide
211	(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one
212	(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide
213	(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one
214	(S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
215	(S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one
216	(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
217	(S)-2-amino-N-cyclohexyl-3-(4-((3-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide

Ex. N.	Chemical Name
218	(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide
219	(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide
220	(S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile
221	(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide
222	(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-(1-methylpiperidin-4-yl)propanamide
223	4-(4-((S)-2-amino-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile
224	(S)-4-(4-(2-amino-3-oxo-3-(4-(pyridin-2-yl)methyl)piperazin-1-yl)propyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile
225	(S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide
226	(S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one
227	(S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-N-cyclohexylpropanamide
228	(S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one
229	(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3,5-difluorophenyl)-2-amino-N-cyclohexylpropanamide
132A	First eluting single enantiomer of 2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
132B	Second eluting single enantiomer of 2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one
8A	First eluting diastereoisomer of (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one
8B	Second eluting diastereoisomer of (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one
91A	First eluting enantiomer of 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide
91B	Second eluting enantiomer of 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide
57A	First eluting enantiomer of 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide
57B	Second eluting enantiomer of 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide

The compounds of the invention, including all the compounds hereabove listed, can be prepared from readily available starting materials using the following general methods and procedures or by using slightly modified processes readily available to those of ordinary skill in the art. Although a particular embodiment of the present invention may be shown or described herein, those skilled in the art will recognize that all embodiments or aspects of the present invention can be prepared using the methods described herein or by using other known methods, reagents and starting materials. When typical or preferred process conditions (i.e. reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated.

While the optimum reaction conditions may vary depending on the particular reactants or solvent used, such conditions can be readily determined by those skilled in the art by routine optimization procedures.

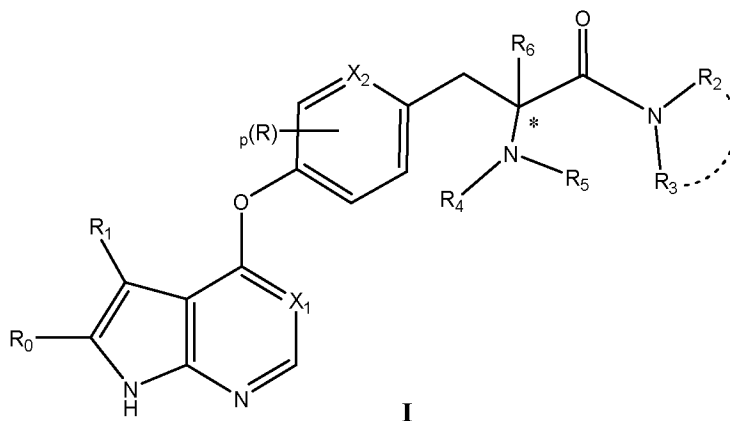
Thus, processes of preparation described below and reported in the following schemes should not be viewed as limiting the scope of the synthetic methods available for the preparation of the compounds of the invention.

In some cases a step is needed in order to mask or protect sensitive or reactive moieties, generally known protective groups (PG) could be employed, in accordance to general principles of chemistry (Protective group in organic syntheses, 3rd ed. T. W. Greene, P. G. M. Wuts).

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

Compounds of formula **I** contain at least one stereogenic centre, as marked as asterisk * in the picture below.

41



Enantiomerically pure compounds can be prepared according to the reactions described below, by means of enantiomerically pure starting materials and intermediates. Preparation of enantiomerically pure compounds of formula **I** on the carbon carrying –

5 NR₄R₅ (which is marked with asterisk in the picture above) may be accomplished by means of enantiomerically pure intermediates **IV** and **XII** as found in the following schemes. These intermediates may be commercial available or readily produced from commercial sources by those of ordinary skill in the art.

In another approach, enantiomerically pure compounds can be prepared from the

10 corresponding racemates by means of chiral chromatography. Whenever, in compounds of formula **I**, there are two or more stereogenic centres, the structure is then characterized by different stereoisomers. Stereochemically pure compounds may be obtained by chiral separation from a diastereoisomeric mixture, or stepwise by chromatographic separation of diastereoisomers followed by further chiral separation into single stereoisomers.

15 Compounds of formula **I**, wherein R₅ is H, may be prepared according to SCHEME 1 as described hereinafter. The SCHEME 1 provides at least one non limiting synthetic route for the preparation of examples from 1 to 151 and from 225 to 229.

Typical protective groups (PG₁) for protection of the NH of the 5-membered ring of the bicyclic intermediate **II** can be 2-[(trimethylsilyl)ethoxy]methyl (SEM), 4-

20 toluenesulfonyl (Ts) and p-methoxybenzyl (PMB), and anyhow not limiting the use of other protective groups. Intermediate **III** may be prepared from the corresponding intermediate **II** and a suitable reagent for PG₁ introduction, for example Ts-Cl (tosyl chloride), SEM-Cl

([2-(trimethylsilyl)ethoxy]methyl chloride) or PMB-Br (p-methoxybenzyl bromide). Reaction between said components may be carried out in a polar organic solvent such as DMF or DCM, in the presence of a strong base, such as NaH, at RT or lower.

The carboxylic acid of intermediate **IV** may be suitably protected as an ester with PG₂ (for example as the methyl ester) and the amino group protected as a carbamate with PG₃ (for example a Boc group). These transformations may be achieved by using generally well know methods starting from unprotected tyrosine like derivatives.

Intermediate **V** may be obtained from Intermediates **III** and **IV** through a palladium catalyzed O-arylation. For example the reaction may be carried out by reacting the aryl halide intermediate **III** and the phenol derivative **IV** in a suitable organic solvent such as toluene or THF, in the presence of an inorganic base such as K₂CO₃, with a suitable palladium catalytic system such as Pd₂dba₃ / XPhos or another palladium source/phosphine based ligand at high temperature (around 100°C) for a few hours.

In a different approach, intermediate **V** may be obtained with a two-step synthesis starting from intermediate **VIII**. Ipso-substitution of the nitro group of the intermediate **VIII** by the phenol of intermediate **IV**, to give intermediate **VII**, may be carried out in a high boiling organic solvent such as DMSO, at a temperature equal to or higher than 100°C and in the presence of an inorganic base such as K₂CO₃. Intermediate **VII** can be converted into intermediate **V** by removing the chlorine atom by means of heterogeneous palladium catalyzed hydrogenation, by reacting **VII** under a hydrogen atmosphere, in the presence of Pd/C and an organic base such as TEA. Intermediate **VIII** may be prepared similarly to intermediate **III** from a corresponding unprotected heterocycle as described above.

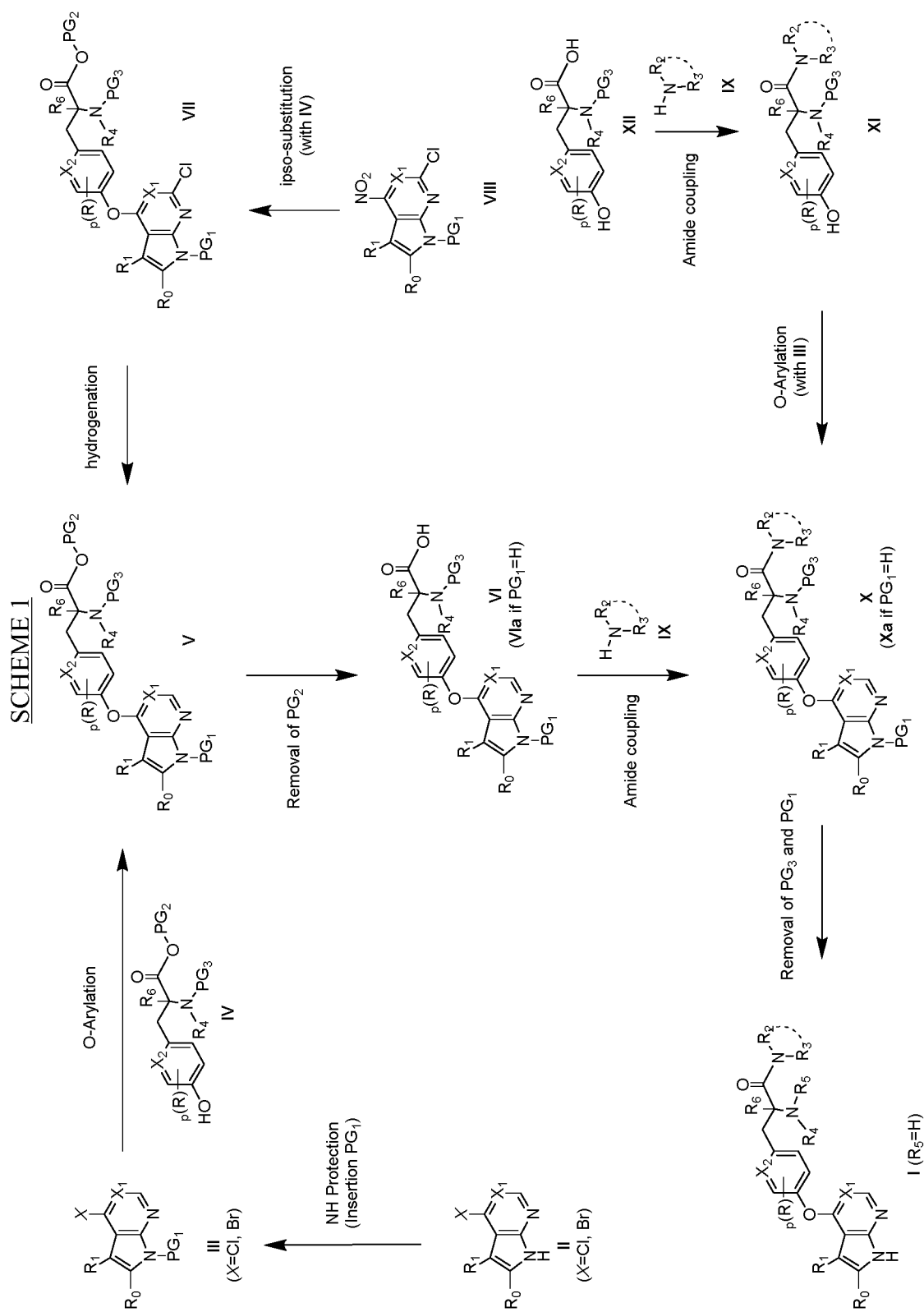
Removal of PG₂ (when PG₂ is a methyl) from intermediate **V** to give the intermediate **VI**, whilst not affecting other protections (PG₁: SEM, Ts or PMB and PG₃: Boc), may be carried out by hydrolysis, using an inorganic base such as LiOH in a mixture of methanol / water, generally at RT and for a time ranging from 1h to overnight. In some cases, for synthetic convenience, the hydrolysis may be carried out at a temperature equal to or higher than 50°C and may lead to concurrent PG₁ cleavage to give intermediate **VIa**.

Intermediate **VIa** can be used in a similar way of intermediate **VI**.

Reaction between intermediate **VI** (or **VIa**) and intermediate **IX** to give the intermediate **X** (or **Xa**) may be carried out under suitable amide coupling reaction conditions. For example, intermediate **VI** (or **VIa**) and **IX** may be reacted in the presence
5 of an activating agent such as COMU or HATU, with an organic base such as DIPEA or TEA, in a suitable organic solvent such as DCM or DMF, and at temperature generally around RT for a time ranging from a few hours to overnight.

Alternatively, intermediate **X** may be prepared from intermediate **XI** and intermediate **III** through palladium catalyzed O-arylation in a similar way to that described
10 above for the preparation of the intermediate **V**. Intermediate **XI** may be obtained by amide coupling of the intermediate **XII** with intermediate **IX** in a similar way as described above for the preparation of intermediate **X**.

Removal of PG₁ and PG₃ from intermediate **X** (or **Xa**, which bears only PG₃), to give compounds of formula **I** (wherein R₅ is H), may be achieved stepwise or concurrently
15 according to the cleavage conditions used (Protective group in organic syntheses, 3rd ed. T. W. Greene, P. G. M. Wuts). For example, an acidic cleavage using a mixture of TFA in an organic solvent such as DCM, can deprotect both Boc and PMB, while SEM may require an extra treatment in concentrated methanolic ammonia or LiOH. The tosyl group (Ts) may be hydrolysed in a solution of inorganic base such as LiOH in water/methanol at
20 temperature equal to or higher than 50°C.



In another embodiment, compounds of formula **I** (wherein R_5 is H, and R_2 and R_3 are taken together with the nitrogen atom they are linked to form a piperazine ring, optionally substituted at the second nitrogen with an R_9) can be prepared according to SCHEME 2, providing at least one non limiting synthetic route for the preparation of examples from 152 to 177.

Intermediate **Xb** indicates a compound of formula **X** wherein R_2R_3 are taken together to form a piperazine ring, in which the second nitrogen is protected by a suitable protective group (indicated as PG_4), that may be orthogonal to PG_1 and PG_3 . A suitable PG_4 group may be represented by a carboxybenzyloxy group (Cbz). Intermediate **Xb** (PG_4 is Cbz) may be converted into intermediate **XIIIa** by catalytic hydrogenation in the presence of a Pd/C catalyst, in an organic solvent such as MeOH or EtOH and at temperature around RT.

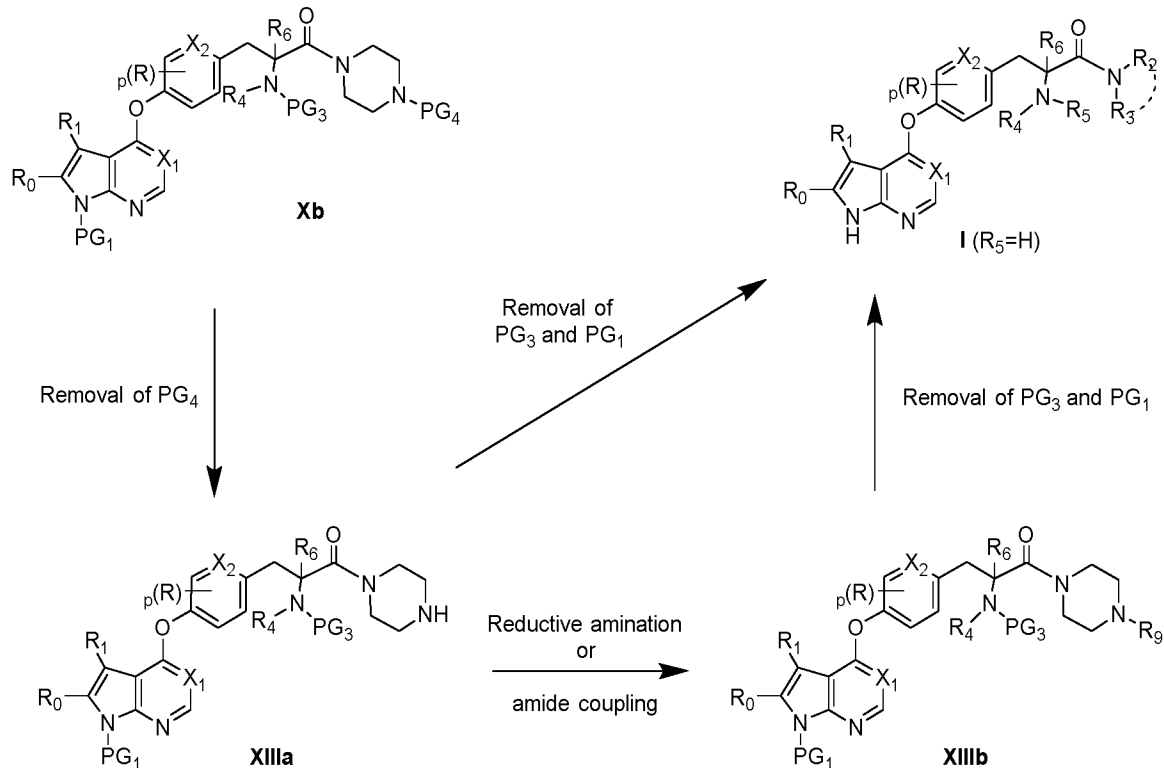
Compounds of formula **I** (wherein R_5 is H, and R_2R_3 are taken together to form a piperazine ring) may be prepared from intermediate **XIIIa** by removal of PG_3 and PG_1 as described for intermediate **X** in SCHEME 1.

Intermediate **XIIIb** may be prepared from intermediate **XIIIa** by introducing group R_9 (as specified above) by means of an amide coupling or a reductive amination. For the amide coupling, intermediate **XIIIa** and a suitable carboxylic acid may be reacted using similar conditions to those already described in SCHEME 1 for the coupling of intermediates **VI** and **IX**. Reductive amination can be performed by reacting intermediate **XIIIa** and a suitable aldehyde, using a reducing agent such as $NaBH(OAc)_3$, $NaBH_3CN$ or $NaBH_4$ and in a suitable organic solvent such as DCE, DCM, THF or MeOH. The reaction proceeds smoothly at room temperature over a couple of hours. It could be useful to react the amine and the aldehyde, to preform the imine, before adding the reducing agent.

Compounds of formula **I** (wherein R_5 is H, and R_2 and R_3 are taken together to form a piperazine ring as above said) can be obtained from intermediate **XIIIb** by removing PG_1 and PG_3 , employing the same cleavage conditions already described in SCHEME 1 for intermediate **X**. It will be apparent to those skilled in the art that the R_9 substituent of

intermediate **XIIIb** may be further elaborated prior to deprotection of PG₁ and PG₃ to give compounds of formula **I**. For example, if R₉ is a 3-(methoxycarbonyl)phenyl)methyl or a methoxycarbonylheteroarylmethyl moiety (for example 5-(methoxycarbonyl)2-furanylmethyl), it can be readily converted into a corresponding amide in a two-step process including a methyl ester hydrolysis and an amide coupling.

SCHEME 2



In another embodiment of the present invention, compounds of formula **I** may be prepared according to SCHEME 3. The SCHEME 3 provides at least one non limiting synthetic route for the preparation of examples from 178-185.

Intermediate **V** (wherein R₄ is H) may be converted into intermediate **XIV** by removing PG₃. For example, when PG₁ is a Ts and PG₃ a Boc, the selective removal of PG₃ may be achieved by acidic cleavage using a mixture of TFA and an organic solvent such as DCM. Intermediate **XIV** may be then converted into intermediate **XV** by introducing R₄ and/or R₅ with an amide coupling or a reductive amination. Amide coupling may be performed by reacting intermediate **XIV** and a suitable carboxylic acid using similar conditions to those already described in SCHEME 1 for the coupling of intermediates **VI**

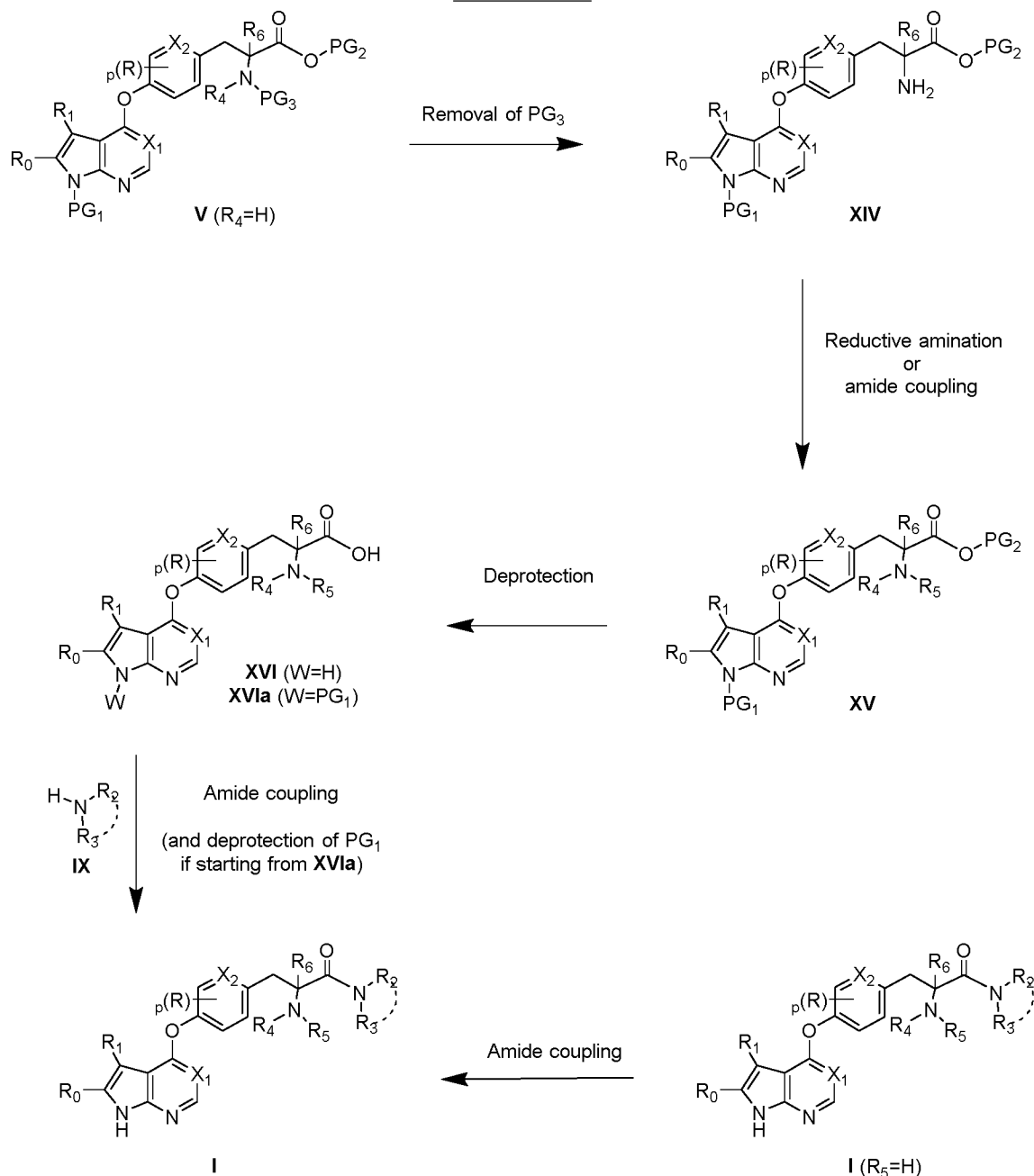
and **IX**. Reductive amination can be performed by reacting intermediate **XIV** and a suitable aldehyde in a similar way to what described for intermediate **XIIIa** of SCHEME 2. Alternatively, reductive amination on intermediate **XIV** may be performed by catalytic hydrogenation of the in situ generated imine, in the presence of a catalyst such as Pd/C and
5 in an alcoholic solvent such as MeOH or EtOH.

Intermediate **XV** may be converted into intermediate **XVI** or **XVIa** by using similar conditions to those already described for the removal of PG₂ and PG₁, or converted into **XVIa** using selective deprotection conditions to remove PG₂ only.

Compounds of formula **I** may be obtained from an amide coupling of intermediate
10 **XVI** (or **XVIa**) and **IX**, employing the same conditions already described in SCHEME 1. Where intermediate **XVIa** is used in the amide coupling, it will be necessary to remove PG₁, as already described in SCHEME 1.

Alternatively, compounds of formula **I** (wherein R₄ is an acyl moiety e.g. heterocycloalkylcarbonyl or cycloalkylcarbonyl), may be obtained by converting a
15 corresponding compound (wherein R₄= H), via an amide coupling with a suitable carboxylic acid, in a similar way to what described in SCHEME 1.

SCHEME 3



In another embodiment of the present invention, compounds of formula **I** (wherein $R_5=H$, R_1 is halogen $X=Cl, Br, I$, or CN or e.g. aryl, heteroaryl, hydroxyalkynyl, cycloalkyl and cycloheteroalkyl and further optionally substituted), may be prepared according to SCHEME 4 providing at least one non limiting synthetic route for the preparation of examples from 186 to 206 and from 217 to 224.

Intermediate **VII** (wherein R_1 is H) may be converted into the intermediate **XVII** by an electrophilic halogenation with the corresponding NXS (N-halo succinimide, $X: Cl$,

Br or I) carried out in an organic solvent such as MeCN and at temperature around RT for a few hours. Intermediate **XVII** may be converted in a two-step synthesis into intermediate **XVIII**. First, PG₂ is removed and then the resulting carboxylic acid intermediate is coupled with amine **IX** under amide coupling conditions. Both removal of PG₂ and amide coupling may be performed using similar conditions to what has already been described in SCHEME 1.

In a different approach, intermediate **XVIII** may be obtained from intermediate **X** (wherein R₁ is H) by halogenation, in a similar way to that already described above for conversion of **VII** into **XVII**.

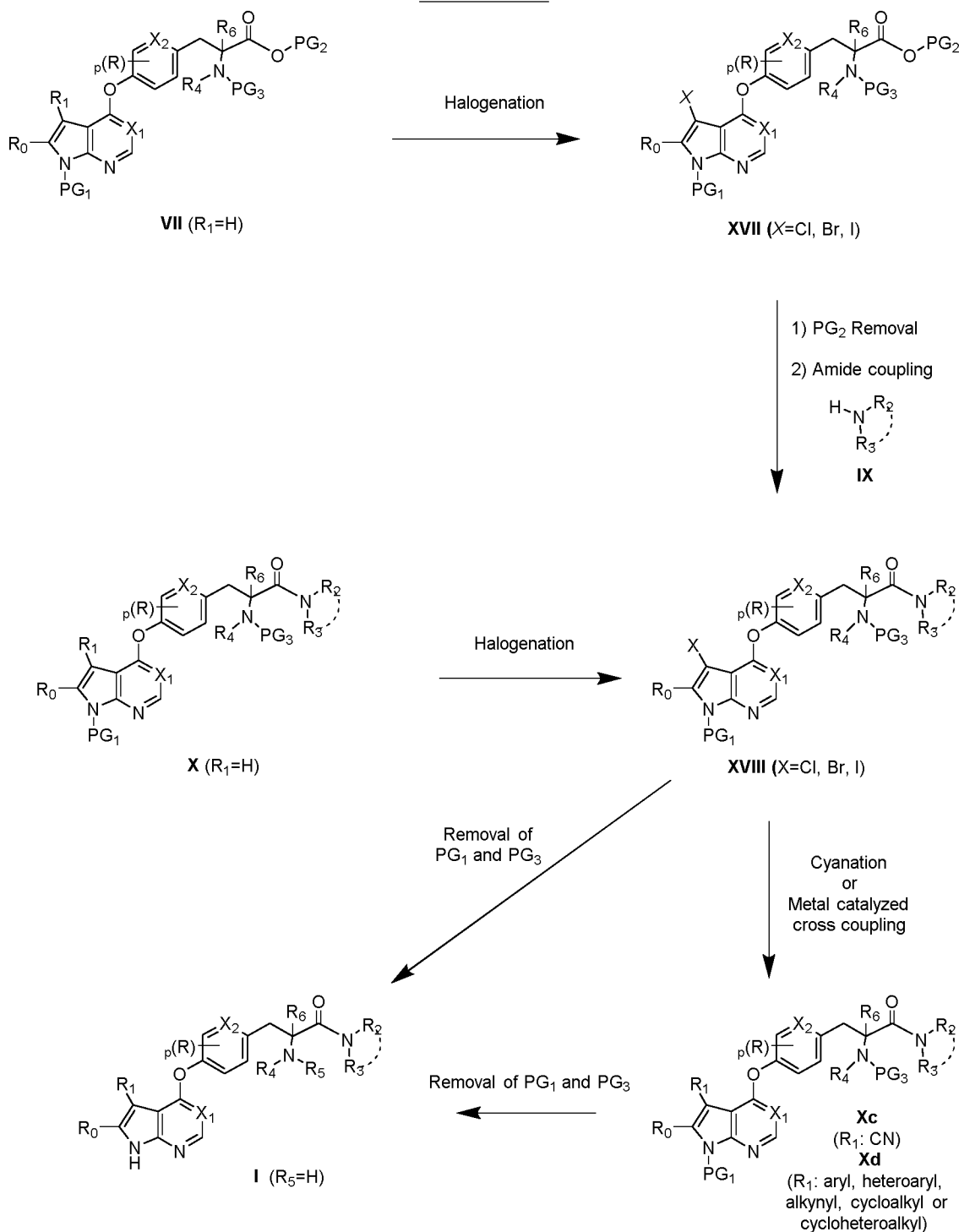
Conversion of intermediate **XVIII** into intermediate **Xc** (when R₁ is CN) may be carried out by metal catalyzed cyanation. For example, intermediate **XVIII** may be reacted with zinc cyanide in the presence of a Pd catalyst, such as Pd₂(dba)₃ / 1,1'-ferrocenediylbis(diphenylphosphine), in an organic solvent such as DMF, and at a temperature higher than 100°C for times up to overnight or longer, to give intermediate **Xc**.

Intermediate **XVIII** can be alternatively converted into intermediate **Xd** by introducing an R₁ group (aryl, heteroaryl, hydroxyalkynyl, cycloalkyl or cycloheteroalkyl) by a palladium catalyzed cross coupling reaction such as Sonogashira, Suzuki or others described in the reference hereinafter (Strategic application of named reactions in organic synthesis, L. Kurti, B. Czako, Ed. 2005). For example, a Sonogashira coupling may be performed by heating the intermediate **XVIII** and a suitable primary alkyne in the presence of a Pd catalyst such as PdCl₂(dppf)₂ DCM adduct or tetrakis(triphenylphosphine)palladium (0), in the presence of copper iodide (I), and a base such as trimethylamine, in an organic solvent such as THF, at a temperature around 90°C or higher and for a time up to overnight or longer. A Suzuki coupling can be executed for example by heating intermediate **XVIII** and a suitable boronic acid or pinacolate derivative in a mixture of water/organic solvent such as DME or THF, in the presence of a Pd catalyst such as PdCl₂(dppf)₂ DCM adduct, with an inorganic base such as an alkaline carbonate, at a temperature around 90°C or higher and for a time up to overnight or longer.

Intermediates **XVIII**, **Xc**, and **Xd** may be converted into compounds of formula **I**, wherein respectively R_1 is a halogen (Cl, Br or I), or a cyano group (CN), or an aryl, heteroaryl, alkynyl, cycloalkyl or cycloheteroalkyl, by using similar methods to what has been already described in SCHEME 1 for removal of PG_1 and PG_3 .

5

SCHEME 4



In another embodiment, compounds of formula **I** (wherein R_1 is $-CH_2OH$ or $-$

CH₂CH₂OH) may be prepared following Scheme 5. The Scheme 5 provides at least one non limiting synthetic route for the preparation of examples from 207 to 216 and from 225 to 229.

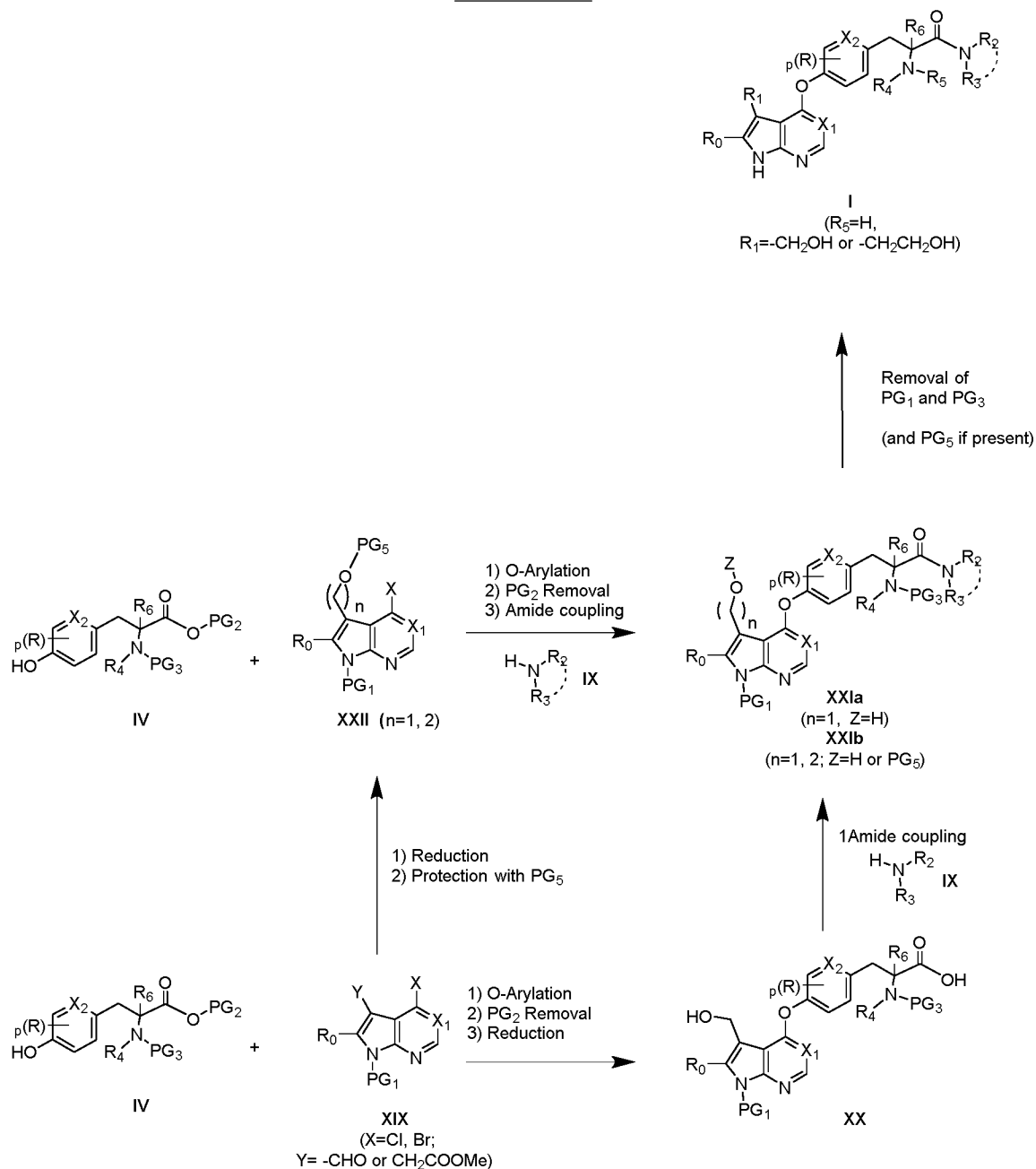
Compounds of formula **I** (wherein R₁ is –CH₂OH or –CH₂CH₂OH) may be prepared from intermediate **XXIa** and/or **XXIb**, by removal of PG₁ and PG₃, in the same way as described for intermediate **X** (SCHEME 1). In the case of an intermediate **XXIb**, which bears a protective group PG₅, the said group can be cleaved under the same conditions as PG₁ and PG₃.

Intermediate **XXIa** may be obtained by an amide coupling of intermediates **XX** and **IX** in a similar way to that described for intermediate **X** (SCHEME 1). Intermediate **XX** may be prepared starting from intermediate **IV** and intermediate **XIX** (wherein Y is CHO) using a palladium catalyzed O-arylation, followed by PG₂ removal as described in SCHEME 1. The resulting aldehyde intermediate can be reduced, for example by sodium borohydride in a mixture of organic solvents such as DCM/MeOH at RT for times up to overnight or longer, to afford intermediate **XX**.

Intermediate **XXIb** may be prepared from intermediate **IV** and **XXII** following the same synthetic sequence described for transforming **III** and **IV** into **X** (SCHEME 1), including O-arylation of **XXII** with **IV**, followed by deprotection of PG₂ and amide coupling with **IX**. Intermediate **XXII** can be prepared from intermediate **XIX** by a two-step synthesis. Reduction of the carbonyl moiety included in Y can be performed in the same way as described in this scheme for intermediate **XX**. The resulting alcohol intermediate may be protected with PG₅ (for example TBDMS) to give intermediate **XXII**, by using generally known methods.

Intermediate **XIX** can be prepared in a similar way of intermediate **III** (SCHEME 1).

SCHEME 5



The compounds of the invention are inhibitors of kinase activity, in particular Rho-kinase activity. Generally speaking, compounds which are ROCK inhibitors may be
 5 useful in the treatment of many disorders associated with ROCK enzymes mechanisms.

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

(PAH).

In another embodiment, the disorder that can be treated by the compound of the present invention is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease such as idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

In a further embodiment, the disorder is selected from idiopathic pulmonary fibrosis (IPF) and pulmonary arterial hypertension (PAH).

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

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

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

Various solid oral dosage forms can be used for administering compounds of the

invention including such solid forms as tablets, gelcaps, capsules, caplets, granules, lozenges and bulk powders. The compounds of the present invention can be administered alone or combined with various pharmaceutically acceptable carriers, diluents (such as sucrose, mannitol, lactose, starches) and known excipients, including suspending agents, solubilizers, buffering agents, binders, disintegrants, preservatives, colorants, flavorants, lubricants and the like. Time release capsules, tablets and gels are also advantageous.

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

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

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

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

For the treatment of the diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation.

Inhalable preparations include inhalable powders, propellant-containing metering

aerosols or propellant-free inhalable formulations.

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

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

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

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

The compounds of the invention can be administered as the sole active agent or in combination (i.e. as co-therapeutic agents administered in fixed dose combination or in combined therapy of separately formulated active ingredients) with other pharmaceutical active ingredients selected from organic nitrates and NO donors; inhaled NO; stimulator of
20 soluble guanylate cyclase (sGC); prostacilin analogue PGI₂ and agonist of prostacyclin receptors; compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP), such as inhibitors of phosphodiesterases (PDE) 1 , 2, 3, 4 and/or 5, especially PDE 5 inhibitors; human neutrophilic elastase inhibitors; compounds inhibiting the signal transduction cascade, such
25 as tyrosine kinase and/or serine/threonine kinase inhibitors; antithrombotic agents, for example platelet aggregation inhibitors, anticoagulants or profibrinolytic substances; active substances for lowering blood pressure, for example calcium antagonists, angiotensin II antagonists, ACE inhibitors, endothelin antagonists, renin inhibitors, aldosterone synthase

inhibitors, alpha receptor blockers, beta receptor blockers, mineralocorticoid receptor antagonists; neutral endopeptidase inhibitor; osmotic agents; ENaC blockers; anti-inflammatories including corticosteroids and antagonists of chemokine receptors; bronchodilators for example beta2agonist and muscarinic antagonists; antihistamine drugs; anti-tussive drugs; antibiotics such as macrolide and DNase drug substance and selective cleavage agents such as recombinant human deoxyribonuclease I (rhDNase); agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroxylase 1 (TPH1) inhibitors and multi-kinase inhibitors.

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

The dosages of the compounds of the invention depend upon a variety of factors including the particular disease to be treated, the severity of the symptoms, the route of administration, the frequency of the dosage interval, the particular compound utilized, the efficacy, toxicology profile, and pharmacokinetic profile of the compound.

Advantageously, the compounds of formula (I) can be administered for example, at a dosage comprised between 0.001 and 1000 mg/day, preferably between 0.1 and 500 mg/day.

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

A pharmaceutical composition comprising a compound of the invention suitable to

be administered by inhalation, such as inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

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

The following examples illustrate the invention in more detail.

PREPARATIONS OF INTERMEDIATES AND EXAMPLES

General Experimental Details

Reactions were not carried out under an inert atmosphere unless specified and all
10 solvents and commercial reagents were used as received.

Purification by chromatography refers to purification using the CombiFlash® Companion purification system or the Biotage SP1 purification system. Where products were purified using an Isolute® SPE Si II cartridge, 'Isolute SPE Si cartridge' refers to a pre-packed polypropylene column containing unbonded activated silica with irregular
15 particles with average size of 50 µm and nominal 60Å porosity. Fractions containing the required product (identified by TLC and/or LCMS analysis) were pooled and concentrated *in vacuo*. Where an SCX-2 cartridge was used, 'SCX-2 cartridge' refers to an Isolute® pre-packed polypropylene column containing a non-end-capped propylsulphonic acid functionalised silica strong cation exchange sorbent. Where HPLC was used for
20 purification (Purification by MDAP) fractions containing the required product (identified by TLC and/or LCMS analysis) were pooled and the solvent removed using a Biotage EV10 Evaporator. Alternatively the pooled product fraction was lyophilised.

NMR spectra were obtained on a Varian Unity Inova 400 spectrometer with a 5 mm inverse detection triple resonance probe operating at 400 MHz or on a Bruker Avance DRX
25 400 spectrometer with a 5 mm inverse detection triple resonance TXI probe operating at 400 MHz or on a Bruker Avance DPX 300 spectrometer with a standard 5 mm dual frequency probe operating at 300 MHz or on a Bruker Fourier 300 spectrometer with a 5 mm dual probe operating at 300 MHz. Shifts are given in ppm relative to tetramethylsilane.

Chemical Names for examples and intermediates were generated with Structure To Name Enterprise 12.0 CambridgeSoft (Perkin Elmer).

Solutions of common inorganic salts used in workups are aqueous solutions. Brine refers to a saturated aqueous solution of NaCl. Unless otherwise specified.

5 LC-MS Method 1

Waters Micromass ZQ2000 mass spectrometer with a C18-reverse-phase column (100 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

10	Gradient – Time	flow (mL/min)	%A	%B
	0.00	0.4	95	5
	0.40	0.4	95	5
	6.00	0.4	5	95
	6.80	0.4	5	95
15	7.00	0.4	95	5
	8.00	0.4	95	5

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 2

20 Waters Micromass ZQ2000 mass spectrometer with a C18-reverse-phase column (100 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% aqueous ammonia; B: MeCN + 0.1% aqueous ammonia.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
25	0.00	0.4	95	5
	0.40	0.4	95	5
	6.00	0.4	5	95
	6.80	0.4	5	95
	7.00	0.4	95	5
30	8.00	0.4	95	5

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 3

- 5 Quattro Micro Mass Spectrometer with a C18-reverse-phase column (100 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
	0.00	0.4	95	5
10	0.40	0.4	95	5
	6.00	0.4	5	95
	6.80	0.4	5	95
	7.00	0.4	95	5
	8.00	0.4	95	5

- 15 Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 4

- 20 QDa Mass Spectrometer with a C18-reverse-phase column (50 × 2.1 mm Acquity CSH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
	0.00	1	97	3
	1.50	1	1	99
25	1.90	1	1	99
	2.00	1	97	3
	2.50	1	97	3

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 5

QDa Mass Spectrometer with a C18-reverse-phase column (50 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 40°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

5 Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
	0.00	1	97	3
	1.50	1	1	99
	1.90	1	1	99
10	2.00	1	97	3
	2.50	1	97	3

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 6

15 QDa Mass Spectrometer with a C18-reverse-phase column (50 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 50°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
20	0.00	1	97	3
	1.50	1	1	99
	1.90	1	1	99
	2.00	1	97	3
	2.50	1	97	3

25 Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

LC-MS Method 7

Waters Platform LC with a C18-reverse-phase column (30 × 4.6 mm Phenomenex

Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
5	0.00	2	95	5
	0.50	2	95	5
	4.50	2	5	95
	5.50	2	5	95
	6.00	2	95	5

10 Detection-MS, ELS, UV (100 µl split to MS with in-line UV detector)

MS ionisation method-Electrospray (positive and negative ion).

LC-MS Method 8

QDa Mass Spectrometer with a C18-reverse-phase column (50 × 2.1 mm Acquity BEH with 1.7 µm particle size) maintained at 50°C, elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
	0.00	1	97	3
	1.50	1	1	99
20	1.90	1	1	99
	2.00	1	97	3
	2.50	1	97	3

Detection-MS, UV PDA

MS ionisation method-Electrospray (positive/negative ion).

25 LC-MS Method 9

QZ Mass Spectrometer with a C18-reverse-phase column (30 × 4.6 mm Phenomenex Luna with 3 µm particle size), elution with A: water + 0.1% formic acid; B: MeCN + 0.1% formic acid.

Gradient:

	Gradient – Time	flow (mL/min)	%A	%B
	0.0	2	95	05
	0.3	2	95	05
5	4.3	2	05	95
	5.3	2	05	95
	5.8	2	95	05
	6.0	2	95	05

Detection-MS, UV PDA

10 MS ionisation method-Electrospray (positive/negative ion).

MDAP Method (acidic)

Agilent Technologies 1260 Infinity purification system with an XSELECT CSH

Prep C18 column (19 x 250 mm, 5 µm OBD) maintained at RT

15 Mobile Phase A: 0.1% aqueous formic acid
 Mobile Phase B: 0.1% formic acid in acetonitrile
 Flow Rate: 20 ml/min
 Gradient Program: 10%-95%, 22 min, centered around a specific focused gradient

20 Sample: Injection of a 20-60 mg/ml solution in DMSO (+ optional formic acid and water)

MDAP Method (basic)

Agilent Technologies 1260 Infinity purification system with an XBridge Prep C18

OBD column (19 x 250 mm, 5 µm OBD) maintained at RT

25 Mobile Phase A: 0.1% aqueous ammonia
 Mobile Phase B: 0.1% ammonia in acetonitrile
 Flow Rate: 20 ml/min
 Gradient Program: 10%-95%, 22 min, centered around a specific focused gradient

Sample: Injection of a 20-60 mg/ml solution in DMSO + optional formic acid and water)

SFC Methods

Supercritical Fluid Chromatography (SFC) was carried out using either a Waters
5 Thar Prep100 preparative SFC system (P200 CO₂ pump, 2545 modifier pump, 2998 UV/VIS detector, 2767 liquid handler with Stacked Injection Module) or a Waters Thar Investigator semi preparative system (Waters Fluid Delivery Module, 2998 UV/VIS detector, Waters Fraction Collection Module). The column and isocratic method used is indicated for each compound and the single enantiomers were analysed using the methods
10 given. Some of the compounds may have gone through a second purification process in order to achieve the required % ee purity.

Preparative HPLC Method (acidic conditions)

Where compounds were purified by HPLC they were carried out on a C18-reverse-phase column (250 × 21.2 mm Phenomenex Kinetex with 5 µm particle size). Specific eluting
15 mixtures are described and, unless otherwise stated, peaks were detected by UV (254 nm). Fractions containing the pure product were generally combined and freeze-dried to give a solid.

Preparative HPLC Method (basic conditions)

Where compounds were purified by HPLC they were carried out on a C18-reverse-phase column (250 × 21.2 mm Phenomenex Kinetex EVO with 5 µm particle size). Specific
20 eluting mixtures are described and, unless otherwise stated, peaks were detected by UV (254 nm). Fractions containing the pure product were generally combined and freeze-dried to give a solid.

Chiral HPLC (Method A)

Enantiomers were separated by chiral HPLC using a Chiralpak IC column (21 x 250
25 mm, 5 µm) and eluting with 15% ethanol in heptane (with 0.5% DEA) at a flow rate of 18 mL/min.

Abbreviations used in the experimental section:

COMU (1-Cyano-2-ethoxy-2-

oxoethylidenaminoxy)dimethylaminomorpholino-carbenium hexafluorophosphate

	DCE	1,2-Dichloroethane
	DCM	Dichloromethane
	DEA	Diethylamine
5	DIPEA	Di-isopropylethylamine
	DME	1,2-Dimethoxyethane
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	Dimethylsulphoxide
	h	Hour(s)
10	HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)
	HPLC	High performance liquid chromatography
	IMS	Industrial methylated spirits
	LCMS	Liquid chromatography-mass spectrometry
15	MDAP	Mass-directed autopurification
	MeCN	Acetonitrile
	NBS	N-Bromosuccinimide
	NCS	N-Chlorosuccinimide
	NIS	N-Iodosuccinimide
20	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium(0)
	Pd ₂ (dppf) ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
	Rt	Retention time
	RT	Room temperature
	SFC	Supercritical Fluid Chromatography
25	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

In the procedures that follow, some of the starting materials are identified through

an “Intermediate” or “Example” number with indications on step number. This is provided merely for assistance to the skilled chemist.

When reference is made to the use of a “similar” or “analogous” procedure, as will be appreciated by those skilled in the art, such a procedure may involve minor variations, for example reaction temperature, reagent/solvent amount, reaction time, work-up conditions or chromatographic purification conditions.

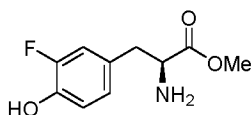
The stereochemistry of the compounds in the Examples, where indicated, has been assigned on the assumption that absolute configuration at resolved stereogenic centers of starting materials is maintained throughout any subsequent reaction conditions.

The ee% (enantiomeric excess) was measured by chiral LC or SFC methods described for Examples 8, 55, 57, 91 and 132. These methods are considered examples for the analytical methods to be used for the determination of ee% .

Unless otherwise stated, where absolute configuration (R) or (S) is reported in the compound name, ee% has to be considered equal or greater than 90%. For those Examples having a measured value of ee% less than 90, the exact value was reported. Wherein the measure of ee% has not been determined , they were marked as n.d. (not determined).

Example 1

Step A



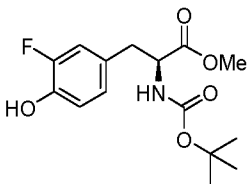
Methyl (S)-2-amino-3-(3-fluoro-4-hydroxyphenyl)propanoate (Intermediate 1A-a)

3-Fluoro-L-tyrosine (6.0 g, 30.12 mmol) was suspended in methanol (120 mL) and the mixture was cooled in an ice bath. Thionyl chloride (11 mL, 150.6 mmol) was added dropwise. The mixture was allowed to warm to RT and then stirred overnight. The solvent was evaporated and the residue dissolved in water (50 mL). After basifying the mixture using saturated aqueous sodium hydrogen carbonate, the product was extracted into ethyl acetate (4 x 40 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated

to give the desired product as a beige solid (4.55 g).

LCMS (Method 4): $R_t = 0.65$ min, m/z 214.1 $[M+H]^+$

Step B

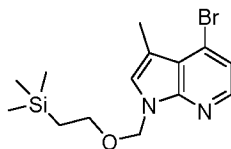


5 **Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-hydroxyphenyl)propanoate (Intermediate 1B-a)**

Intermediate 1A-a (4.55 g, 21.34 mmol) was suspended in a mixture of DCM (153 mL) and THF (77 mL). The mixture was cooled in an ice bath and di-tert-butyl dicarbonate (5.12 g, 23.47 mmol) was added. The reaction mixture was allowed to warm to RT and stirred for 4 h. The solvent was evaporated *in vacuo* and the crude product was chromatographed on a 120 g Si cartridge eluting with 0-10% 2M methanolic ammonia in DCM. Intermediate 1B-a was obtained as a yellow gum (5.96 g).

LCMS (Method 4): $R_t = 1.29$ min, m/z 336.2 $[M+Na]^+$

Step C

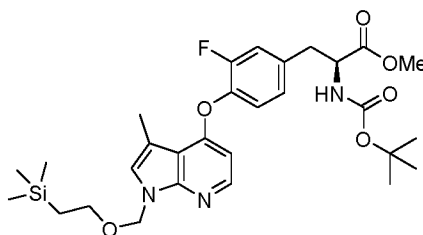


15 **4-Bromo-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 1C-a)**

4-Bromo-3-methyl-7-azaindole (4.0 g, 18.95 mmol) was dissolved in DMF (37 mL) and the solution was cooled in an ice bath. Sodium hydride (60% on mineral oil, 1.14 g, 28.43 mmol) was added and the mixture was stirred under a stream of nitrogen for 1 h. 2-(Trimethylsilyl)ethoxymethyl chloride (4.0 mL, 22.74 mmol) was added dropwise and then the reaction mixture was stirred for a further 30 min. After quenching with water (20 mL), the product was extracted into ethyl acetate (3 x 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a 120 g Si cartridge eluting with 0-25% ethyl acetate in cyclohexane to give Intermediate 1C-a as a colourless oil (3.78 g).

LCMS (Method 6): $R_t = 1.90$ min, m/z 341.1/343.0 $[M+H]^+$

Step D



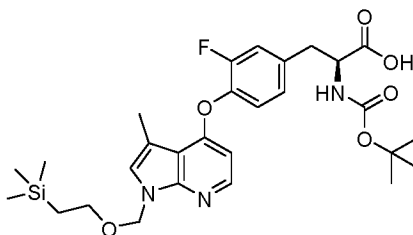
5 **Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-propanoate (Intermediate 1D-a)**

A mixture of Intermediates 1B-a (5.96 g, 19.02 mmol) and 1C-a (6.09 g, 17.84 mmol), $Pd_2(dba)_3$ (0.82 g, 0.89 mmol), XPhos (0.85 g, 1.78 mmol), and potassium carbonate (5.42 g, 39.25 mmol) in toluene (224 mL) was sonicated for 5 min under a blanket of argon. The mixture was heated at $100^\circ C$ for 3 h, and then allowed to cool to RT before filtering through Celite[®]. The solvent was evaporated and the residue was taken up into water (40 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4) and evaporated. The crude product was chromatographed on a 300 g Si cartridge eluting with 0-50% ethyl acetate in cyclohexane.

15 The product was obtained as a beige solid (4.85 g).

LCMS (Method 4): $R_t = 1.88$ min, m/z 574.4 $[M+H]^+$

Step E



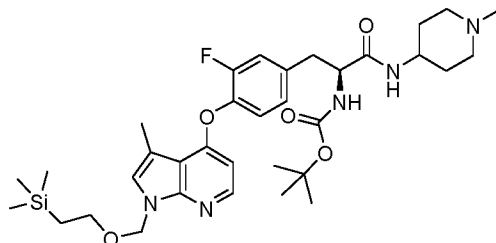
20 **(S)-2-((tert-Butoxycarbonyl)amino)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 1E-a)**

Intermediate 1D-a (4.85 g, 8.45 mmol) was dissolved in a mixture of methanol (42

mL), water (42 mL) and THF (21 mL). Lithium hydroxide hydrate (1.06 g, 25.35 mmol) was added and the reaction mixture was stirred at RT for 10 min. The solvent was reduced and the product was extracted into ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried (Na₂SO₄) and evaporated to give a beige solid (4.74 g).

5 LCMS (Method 6): Rt = 1.79 min, m/z 560.4 [M+H]⁺

Step F



tert-Butyl (S)-(3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1-methylpiperidin-4-yl)amino)-1-oxopropan-2-yl)carbamate (Intermediate 1F-a)

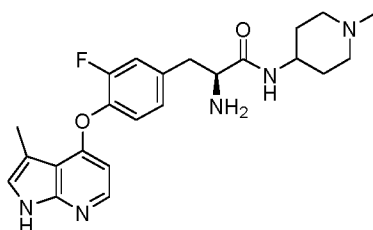
10

Intermediate 1E-a (500 mg, 0.89 mmol), 1-methylpiperidin-4-amine (112 mg, 0.98 mmol) and COMU (457 mg, 1.07 mmol) were dissolved in DCM (15 mL) and DIPEA (0.35 mL, 1.96 mmol) was added. The reaction was stirred at RT for 2.5 h and then a further amount of 4-amino-1-methylpiperidine (55 mg, 0.49 mmol) was added. Stirring was continued for a further 2 h. Water (15 mL) was added and the DCM layer was separated. The aqueous was further extracted with DCM (2 x 10 mL) and the combined organic extracts were dried (Na₂SO₄) and evaporated. The product was purified by chromatography on a 40 g Si cartridge eluting with 0-10% 2M methanolic ammonia in DCM. Intermediate 1F-a was obtained as a yellow solid (418 mg).

15

20 LCMS (Method 4): Rt = 1.27 min, m/z 656.3 [M+H]⁺

Step G



(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide (Example 1)

Intermediate 1F-a (418 mg, 0.64 mmol) was dissolved in a mixture of DCM (7.1 mL) and TFA (7.1 mL), and the reaction was stirred at RT for 4 h. The mixture was diluted with methanol and passed down a 10 g SCX-2 cartridge eluting with methanol and then 2M methanolic ammonia. After standing for 18 h, the ammonia solution was evaporated to give a residue which was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH₄OH added). Example 1 was obtained as a white solid (111 mg).

LCMS (Method 1): Rt = 1.69 min, m/z 425.9 [M+H]⁺

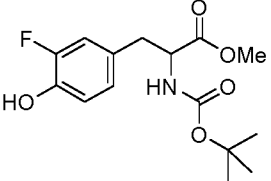
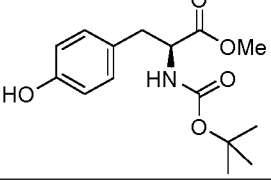
¹H NMR (400 MHz, d₆-DMSO) δ 11.38 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.64 (d, J=7.8 Hz, 1H), 7.28-7.20 (m, 2H), 7.13 (d, J=1.6 Hz, 1H), 7.08 (dd, J=1.3, 8.3 Hz, 1H), 6.16 (d, J=4.8 Hz, 1H), 3.53-3.42 (m, 1H), 3.41-3.35 (m, 1H), 2.87 (dd, J=5.9, 13.3 Hz, 1H), 2.74-2.54 (m, 3H), 2.38 (d, J=1.0 Hz, 3H), 2.12 (s, 3H), 1.97-1.86 (m, 2H), 1.79-1.69 (s, 2H), 1.68-1.57 (m, 2H), 1.43-1.26 (m, 2H).

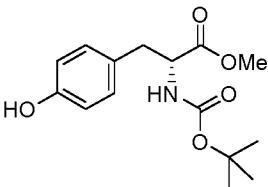
Examples 2 to 130

The following Examples were prepared in a similar way to Example 1 by replacing at each step the appropriate starting materials.

Preparation of Intermediates 1B-b to 1B-e

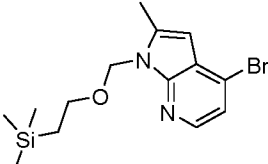
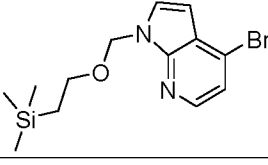
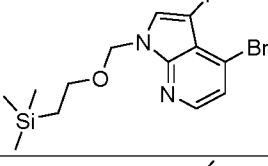
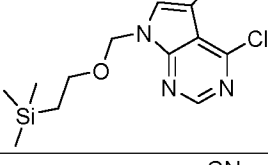
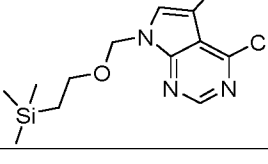
The following intermediates were prepared in a similar manner to Intermediate 1B-a by replacing in Step A of Example 1 the tyrosine with the indicated starting materials.

Intermediate	Starting material	Starting material	LC-MS
1B-b		3-Fluoro-DL-tyrosine	Rt = 1.21 min, m/z 336.2 [M+Na] ⁺ (Method 6)
1B-c		L-Tyrosine	Rt = 3.03 min, m/z 296.1 [M+H] ⁺ (Method 7)

Intermediate	Starting material	Starting material	LC-MS
1B-d		D-Tyrosine	Rt = 1.19 min, m/z 294.0 [M-H] ⁻ (Method 6)

Preparation of Intermediates 1C-b to 1C-f

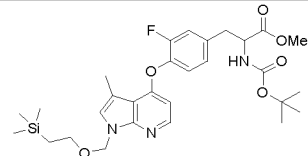
The following intermediates were prepared in a similar manner to Intermediate 1C-a from the indicated starting materials.

Intermediate	Structure	Starting materials	LC-MS
1C-b		4-Bromo-2-methyl-7-azaindole	Rt = 4.60 min, m/z 340.9/342.9 [M+H] ⁺ (Method 9)
1C-c		4-Bromo-7-azaindole	Rt = 1.80 min, m/z 326.9/328.9 [M+H] ⁺ (Method 6)
1C-d		4-Bromo-3-fluoro-7-azaindole	Rt = 1.77 min, m/z 344.9/346.9 [M+H] ⁺ (Method 6)
1C-e		4-Chloro-5-methyl-7H-pyrrolo[2,3-d]pyrimidine	Rt = 2.35 min, m/z 298.1 [M+H] ⁺ (Method 4)
1C-f		4-Chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidine	Rt = 3.81 min, m/z 309.0 [M+H] ⁺ (Method 9)

5

Preparation of Intermediates from 1D-b to 1D-g

The following intermediates were prepared in a similar manner to Intermediate 1D-a from the indicated starting materials.

Intermediate	Structure	Starting materials	LC-MS
1D-b		1B-b and 1C-a	Rt = 1.83 min, m/z 574.3 [M+H] ⁺ (Method 6)

Intermediate	Structure	Starting materials	LC-MS
1D-c		1B-a and 1C-b	Rt = 1.87 min, m/z 574.2 [M+H] ⁺ (Method 6)
1D-d		1B-c and 1C-a	Rt = 1.86 min, m/z 556.2 [M+H] ⁺ (Method 4)
1D-e		1B-c and 1C-c	Rt = 4.67 min, m/z 542.3 [M+H] ⁺ (Method 7)
1D-f		Methyl (tert-butoxycarbonyl)-tyrosinate and -1C-c	Rt = 4.69 min, m/z 542.2 [M+H] ⁺ (Method 7)
1D-g		1B-d and 1C-c	Rt = 4.67 min, m/z 542.4 [M+H] ⁺ (Method 7)
1D-h		1B-c and 1C-d	Rt = 1.84 min, m/z 560.2 [M+H] ⁺ (Method 4)
1D-i		1B-a and 1C-e	Rt = 2.48 min, m/z 575.3 [M+H] ⁺ (Method 6)
1D-j		1B-a and 1C-f	Rt = 2.40 min, m/z 586.3 [M-H] ⁻ (Method 6)

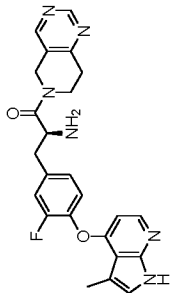
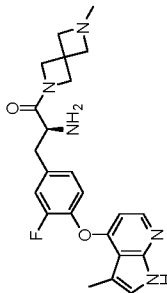
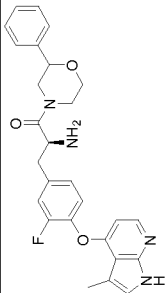
Preparation of Intermediates from 1E-b to 1E-p

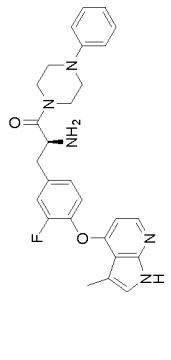
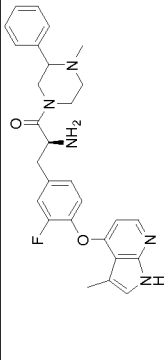
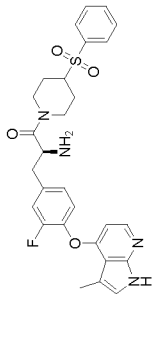
The following intermediates were prepared in a similar manner to Intermediate 1E-a from the indicated starting materials.

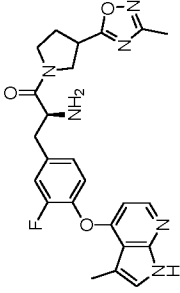
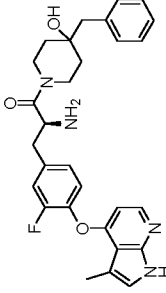
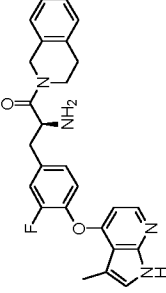
Intermediate	Structure	Starting materials	LC-MS
1E-b		1D-b	Rt = 1.75 min, m/z 560.3 [M+H] ⁺ (Method 6)
1E-c		1D-c	Rt = 1.79 min, m/z 560.2 [M+H] ⁺ (Method 6)
1E-d		1D-d	Rt = 1.77 min, m/z 542.2 [M+H] ⁺ (Method 4)
1E-e		1D-e	Rt = 4.24 min, m/z 528.4 [M+H] ⁺ (Method 7)
1E-f		1D-f	Rt = 4.26 min, m/z 528.2 [M+H] ⁺ (Method 7)
1E-g		1D-g	Rt = 1.74 min, m/z 528.4 [M+H] ⁺ (Method 6)
1E-h		1D-h	Rt = 1.75 min, m/z 546.1 [M+H] ⁺ (Method 4)
1E-i		1D-i	Rt = 1.71 min, m/z 561.3 [M+H] ⁺ (Method 4)
1E-j		1D-j	Rt = 1.68 min, m/z 570.2 [M-H] ⁻ (Method 6)

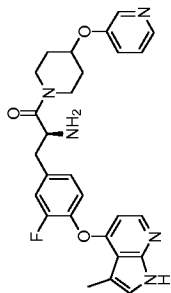
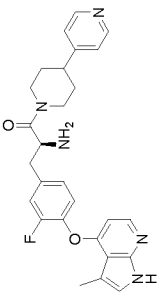
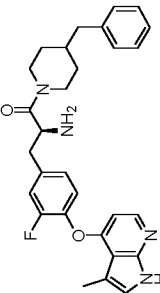
Preparation of Examples

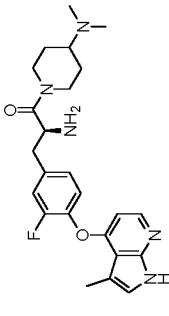
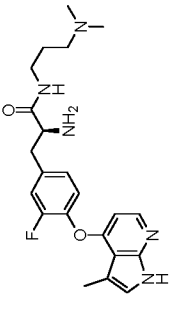
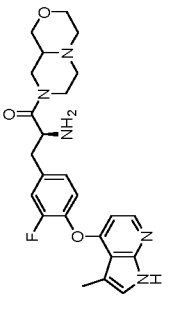
The following examples were prepared in a similar manner to Example 1, following the same synthetic sequence, by replacing in Step F the indicated Intermediate 1E and amine starting materials in the table below.

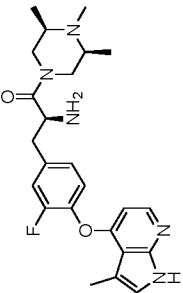
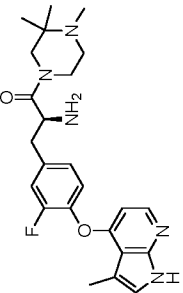
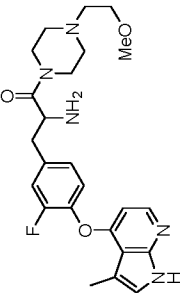
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
2	 (S)-2-amino-1-(7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / 5,6,7,8-tetrahydro-pyrido[4,3-d]-pyrimidine	¹ H NMR (400 MHz, d6-DMSO) δ 11.38 (s, 1H), 8.95-8.93 (m, 1H), 8.71-8.41 (m, 1H), 7.95 (dd, J=5.6, 5.6 Hz, 1H), 7.35-7.05 (m, 4H), 6.12 - 6.01 (m, 1H), 4.79-4.62 (m, 2H), 4.09-3.60 (m, 3H), 3.00-2.67 (m, 4H), 2.38 (d, J=6.9 Hz, 3H), 1.80 (s, 2H).	Rt = 1.96 min, m/z 446.9 [M+H] ⁺ (Method 1)
3	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one	1E-a / 2-methyl-2,6-diaza-spiro[3.3]heptane	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.30-7.23 (m, 2H), 7.14 (s, 1H), 7.09 (dd, J=1.3, 8.3 Hz, 1H), 6.16 (d, J=5.0 Hz, 1H), 4.15 (d, J=9.0 Hz, 1H), 3.87 (d, J=10.2 Hz, 1H), 3.79 (d, J=10.2 Hz, 1H), 3.65 (d, J=9.0 Hz, 1H), 3.39 (dd, J=7.1, 7.1 Hz, 1H), 3.19-3.10 (m, 3H), 3.02 (d, J=7.2 Hz, 1H), 2.77-2.64 (m, 2H), 2.38 (d, J=1.0 Hz, 3H), 2.12 (s, 3H), 1.69 (s, 2H).	Rt = 1.63 min, m/z 424.0 [M+H] ⁺ (Method 1)
4	 (2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylmorpholino)propan-1-one	1E-a / rac-2-phenylmorpholine	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 8.00-7.82 (m, 1H), 7.42-7.06 (m, 9H), 6.17-6.08 (m, 1H), 4.50-4.15 (m, 2H), 4.09-3.87 (m, 3H), 3.76-3.50 (m, 1H), 3.10-2.54 (m, 4H), 2.39-2.34 (m, 3H), 1.81 (s, 2H).	Rt = 2.77/2.81 min, m/z 475.0 [M+H] ⁺ (Method 1)

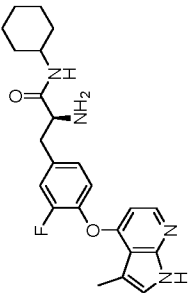
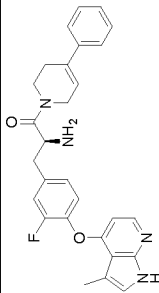
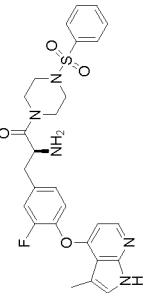
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
5	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenylpiperazin-1-yl)propan-1-one	1E-a / 1-phenylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.37 (s, 1H), 7.82 (d, J=5.4 Hz, 1H), 7.34 (dd, J=1.9, 11.9 Hz, 1H), 7.25-7.19 (m, 3H), 7.15-7.11 (m, 2H), 6.93 (d, J=7.9 Hz, 2H), 6.81 (dd, J=7.3, 7.3 Hz, 1H), 6.08 (d, J=5.3 Hz, 1H), 4.01 (dd, J=6.9, 6.9 Hz, 1H), 3.72-3.49 (m, 4H), 3.15 (d, J=4.7 Hz, 2H), 2.95-2.90 (m, 1H), 2.87-2.69 (m, 3H), 2.34 (d, J=0.9 Hz, 3H), 1.81-1.72 (m, 2H).	Rt = 2.78 min, m/z 474.1 [M+H] ⁺ (Method 1)
6	 (2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methyl-3-phenylpiperazin-1-yl)propan-1-one	1E-a / rac-1-methyl-2-phenylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.00-7.91 (m, 1H), 7.39-7.01 (m, 9H), 6.22-6.11 (m, 1H), 4.48-4.16 (m, 1H), 4.03-3.93 (m, 1H), 3.85-3.59 (m, 1H), 3.01-2.53 (m, 6H), 2.40-2.33 (m, 3H), 2.23-2.03 (m, 1H), 1.90-1.81 (m, 3H), 1.82-1.74 (m, 2H).	Rt = 2.16 min, m/z 488.1 [M+H] ⁺ (Method 1)
7	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one	1E-a / 4-(phenylsulfonyl)-piperidine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.99 (dd, J=5.4, 11.7 Hz, 1H), 7.87-7.82 (m, 2H), 7.78 (q, J=7.9 Hz, 1H), 7.73-7.64 (m, 2H), 7.31 (dd, J=1.2, 11.8 Hz, 1H), 7.21 (dd, J=8.4, 8.4 Hz, 1H), 7.13 (s, 1H), 7.10 (d, J=2.9 Hz, 1H), 6.20-6.11 (m, 1H), 4.48 (d, J=12.3 Hz, 1H), 4.07-4.01 (m, 1H), 3.90 (q, J=6.3 Hz, 1H), 3.60-3.51 (m, 1H), 3.04-2.76 (m, 2H), 2.69-2.54 (m, 2H), 2.38 (d, J=7.9 Hz, 3H), 1.90-1.66 (m, 4H), 1.60-1.12 (m, 2H).	Rt = 2.62 min, m/z 537.1 [M+H] ⁺ (Method 1)

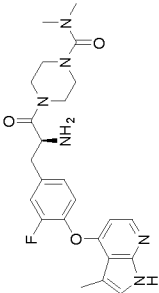
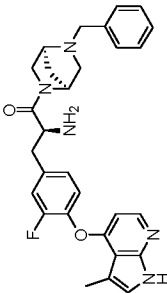
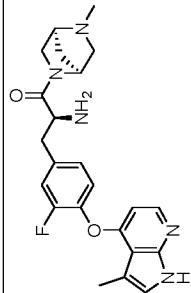
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
8	 (2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one	1E-a / 3-methyl-5-(pyrrolidin-3-yl)-1,2,4-oxadiazole	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.00-7.94 (m, 1H), 7.38-7.18 (m, 2H), 7.15-7.09 (m, 2H), 6.16-6.11 (m, 1H), 3.88-3.66 (m, 3H), 3.57-3.57 (m, 3H), 2.91-2.80 (m, 1H), 2.72-2.62 (m, 1H), 2.38-2.28 (m, 6H), 2.27-1.96 (m, 2H), 1.74 (s, 2H).	Rt = 2.38 min, m/z 465.0 [M+H] ⁺ (Method 1)
9	 (S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / 4-benzylpiperidin-4-ol	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.32-7.06 (m, 9H), 6.16-6.12 (m, 1H), 4.46-4.37 (m, 1H), 4.14-4.08 (m, 1H), 3.97-3.91 (m, 1H), 3.69-3.60 (m, 1H), 3.57-3.56 (m, 1H), 3.23-2.96 (m, 1H), 2.84-2.65 (m, 4H), 2.40-2.29 (m, 3H), 1.72 (s, 2H), 1.52-1.21 (m, 3H), 0.94 (m, 1H).	Rt = 2.70 min, m/z 503.1 [M+H] ⁺ (Method 1)
10	 (S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / 1,2,3,4-tetrahydroisoquinoline	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.37 (s, 1H), 7.94-7.88 (m, 1H), 7.37-7.26 (m, 1H), 7.20-7.10 (m, 7H), 6.10-5.99 (m, 1H), 4.79-4.48 (m, 2H), 4.08-3.98 (m, 1H), 3.79-3.71 (m, 1H), 3.66-3.58 (m, 1H), 2.91-2.66 (m, 4H), 2.37 (s, 3H), 1.79 (s, 2H).	Rt = 2.69 min, m/z 445.0 [M+H] ⁺ (Method 1)

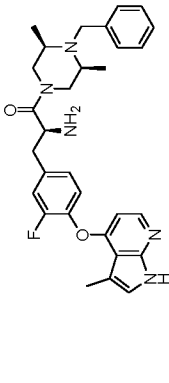
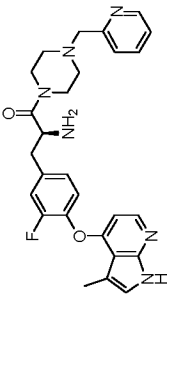
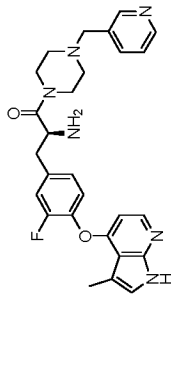
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
11	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yloxy)piperidin-1-yl)propan-1-one	1E-a / 3-(piperidin-4-yloxy)pyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.33-8.25 (m, 1H), 8.18-8.15 (m, 1H), 8.01-7.91 (m, 1H), 7.48-7.39 (m, 1H), 7.37-7.29 (m, 2H), 7.27-7.21 (m, 1H), 7.16-7.09 (m, 2H), 6.16 (t, J=4.1 Hz, 1H), 4.71-4.63 (m, 1H), 4.02-3.87 (m, 2H), 3.85-3.64 (m, 1H), 3.28-3.19 (m, 2H), 2.88-2.79 (m, 1H), 2.74-2.64 (m, 1H), 2.38 (d, J=2.3 Hz, 3H), 2.00-1.68 (m, 4H), 1.69-1.48 (m, 1H), 1.46-1.17 (m, 1H).	Rt = 2.19 min, m/z 490.1 [M+H] ⁺ (Method 1)
12	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one	1E-a / 4-(piperidin-4-yl)pyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.53-8.36 (m, 2H), 8.02-7.86 (m, 1H), 7.37-7.11 (m, 5H), 6.18-6.05 (m, 1H), 4.59-4.53 (m, 1H), 4.13-3.98 (m, 2H), 3.57-3.57 (m, 2H), 3.17-2.90 (m, 1H), 2.89-2.54 (m, 4H), 2.39-2.33 (2xs, 3H), 1.88-1.69 (m, 3H), 1.68-1.39 (m, 1H), 1.36-0.92 (m, 1H).	Rt = 1.93 min, m/z 474.0 [M+H] ⁺ (Method 1)
13	 (S)-2-amino-1-(4-benzylpiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / 4-benzylpiperidine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.97 (dd, J=5.4, 11.2 Hz, 1H), 7.33-7.09 (m, 9H), 6.14 (dd, J=5.4, 14.3 Hz, 1H), 4.38 (t, J=12.3 Hz, 1H), 3.98-3.83 (m, 2H), 3.57 (s, 3H), 2.89-2.57 (m, 3H), 2.39-2.35 (m, 4H), 1.69 (s, 2H), 1.61-1.34 (m, 2H), 1.24-0.95 (m, 1H), 0.84-0.28 (m, 1H).	Rt = 3.17 min, m/z 487.1 [M+H] ⁺ (Method 1)

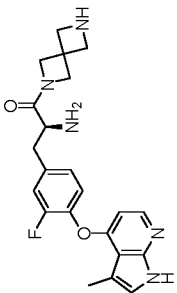
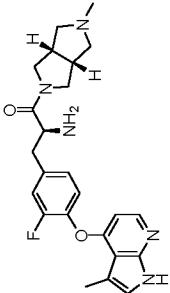
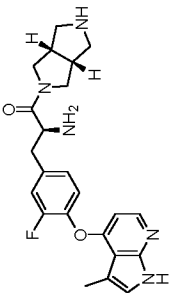
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
14	 (S)-2-amino-1-(4-((dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / N,N-dimethylpiperidine-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.36 (s, 1H), 8.00-7.95 (m, 1H), 7.35-7.19 (m, 2H), 7.15-7.08 (m, 2H), 6.15-6.14 (m, 1H), 4.41-4.32 (m, 1H), 4.02-3.85 (m, 2H), 2.97-2.87 (m, 1H), 2.78 (m, 2H), 2.69-2.57 (m, 1H), 2.38 (d, J=4.8 Hz, 3H), 2.31-2.20 (m, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 1.70-1.66 (m, 4H), 1.38-1.13 (m, 1H), 1.05-0.53 (m, 1H).	Rt = 1.67 min, m/z 440.3 [M+H] ⁺ (Method 1)
15	 (S)-2-amino-N-(3-((dimethylamino)propyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-a / N,N-dimethylpropane-1,3-diamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.36 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.85 (t, J=5.7 Hz, 1H), 7.29-7.20 (m, 2H), 7.15-7.12 (m, 1H), 7.12-7.06 (m, 1H), 6.16 (d, J=4.9 Hz, 1H), 3.41-3.36 (m, 1H), 3.12-2.99 (m, 2H), 2.90 (dd, J=5.7, 13.3 Hz, 1H), 2.71 (dd, J=7.5, 13.2 Hz, 1H), 2.38 (d, J=0.9 Hz, 3H), 2.12 (t, J=7.1 Hz, 2H), 2.08 (s, 6H), 1.75 (s, 2H), 1.51-1.41 (m, 2H).	Rt = 3.27 min, m/z 414.0 [M+H] ⁺ (Method 1)
16	 (2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(hexahydro-pyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propan-1-one	1E-a / rac-octahydro-pyrazino[2,1-c][1,4]oxazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.01-7.97 (m, 1H), 7.35-7.20 (m, 2H), 7.15-7.07 (m, 2H), 6.24-6.13 (m, 1H), 4.42-4.14 (m, 1H), 4.01-3.93 (m, 1H), 3.88-3.58 (m, 3H), 3.54-3.43 (m, 1H), 3.11-3.00 (m, 1H), 2.83-2.54 (m, 6H), 2.38 (s, 3H), 2.20-1.94 (m, 3H), 1.74 (s, 2H).	Rt = 1.87/1.91 min, m/z 454.3 [M+H] ⁺ (Method 1)

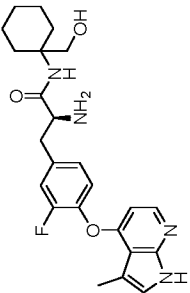
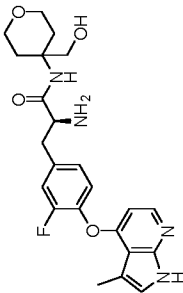
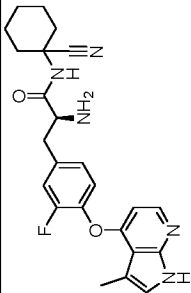
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
17	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one	1E-a / (2S,6R)-1,2,6-trimethyl-piperazine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.99 - 7.96 (m, 1H), 7.34 - 7.27 (m, 1H), 7.27 - 7.20 (m, 1H), 7.16 - 7.12 (m, 1H), 7.11 - 7.06 (m, 1H), 6.19 - 6.13 (m, 1H), 4.23 - 4.16 (m, 1H), 4.12 - 3.96 (m, 1H), 3.83 - 3.65 (m, 1H), 2.79 - 2.65 (m, 3H), 2.38 (d, J=4.1 Hz, 3H), 2.30 - 2.20 (m, 1H), 2.06 (s, 3H), 1.98 - 1.88 (m, 1H), 1.77 - 1.66 (m, 2H), 1.27 - 1.21 (m, 1H), 1.03 - 0.91 (m, 6H).	Rt = 1.67 min, m/z 440.2 [M+H] ⁺ (Method 1)
18	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3,3,4-trimethylpiperazin-1-yl)propan-1-one	1E-a / 1,2,2-trimethyl-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.36-7.28 (m, 1H), 7.26-7.19 (m, 1H), 7.14-7.13 (m, 1H), 7.11-7.07 (m, 1H), 6.15 (t, J=5.9 Hz, 1H), 4.03-3.90 (m, 1H), 3.52-3.37 (m, 2H), 3.06 (dd, J=3.1, 12.4 Hz, 1H), 2.83 (dd, J=6.7, 13.2 Hz, 1H), 2.69 (dd, J=7.2, 13.2 Hz, 1H), 2.39-2.37 (m, 6H), 2.09 (s, 3H), 1.73 (s, 2H), 0.91 (d, J=7.3 Hz, 3H), 0.83 (s, 1H), 0.76 (s, 2H).	Rt = 1.69 min, m/z 440.3 [M+H] ⁺ (Method 1)
19	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-methoxyethyl)piperazin-1-yl)propan-1-one	1E-b / 1-(2-methoxyethyl)piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.30 (dd, J=1.9, 11.9 Hz, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.14-7.08 (m, 2H), 6.16 (d, J=4.8 Hz, 1H), 3.94 (t, J=7.0 Hz, 1H), 3.54-3.48 (m, 1H), 3.43-3.39 (m, 2H), 3.38-3.32 (m, 5H), 3.22 (s, 3H), 2.79 (dd, J=6.7, 13.2 Hz, 1H), 2.68 (dd, J=7.2, 13.1 Hz, 1H), 2.43 (t, J=5.9 Hz, 2H), 2.38 (d, J=1.0 Hz, 3H), 2.23-2.17 (m, 1H), 2.07-1.99 (m, 1H), 1.76-1.76 (m, 2H).	Rt = 1.73 min, m/z 456.2 [M+H] ⁺ (Method 1)

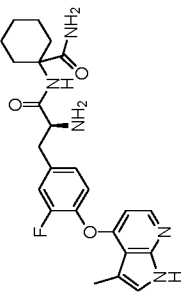
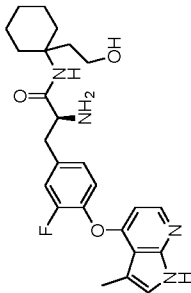
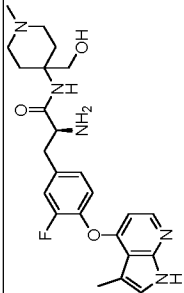
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
20	 (S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-a / cyclohexan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.28-7.20 (m, 2H), 7.15-7.06 (m, 2H), 6.15 (d, J=4.8 Hz, 1H), 3.55-3.46 (m, 1H), 3.38 (t, J=6.7 Hz, 1H), 2.86 (dd, J=6.0, 13.2 Hz, 1H), 2.71 (dd, J=7.3, 13.0 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 1.77 (d, J=1.2 Hz, 2H), 1.69-1.52 (m, 5H), 1.29-1.16 (m, 2H), 1.15-1.02 (m, 3H).	R _t = 2.72 min, m/z 411.3 [M+H] ⁺ (Method 3)
21	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)propan-1-one	1E-a / 4-phenyl-piperidin-4-ol	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.37 (s, 1H), 7.90-7.87 (m, 1H), 7.45-7.11 (m, 9H), 6.21-6.05 (m, 2H), 4.30-4.23 (m, 1H), 4.13-3.92 (m, 3H), 3.71-3.62 (m, 2H), 2.90-2.80 (m, 1H), 2.75-2.66 (m, 1H), 2.44-2.43 (m, 1H), 2.37-2.33 (m, 3H), 1.78 (s, 2H).	R _t = 2.92 min, m/z 471.0 [M+H] ⁺ (Method 1)
22	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperazin-1-yl)propan-1-one	1E-a / 1-(phenylsulfonyl)-piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.74-7.62 (m, 5H), 7.28 (dd, J=1.9, 11.9 Hz, 1H), 7.20-7.14 (m, 2H), 7.06 (q, J=7.8 Hz, 1H), 6.13 (dd, J=0.8, 5.4 Hz, 1H), 3.83 (dd, J=5.8, 7.7 Hz, 1H), 3.73-3.62 (m, 2H), 3.44-3.37 (m, 2H), 3.00-2.93 (m, 2H), 2.85-2.71 (m, 3H), 2.59 (dd, J=8.0, 13.5 Hz, 1H), 2.38 (d, J=1.1 Hz, 3H), 1.67 (s, 2H).	R _t = 2.73 min, m/z 538.0 [M+H] ⁺ (Method 1)

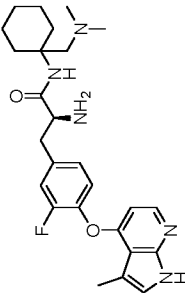
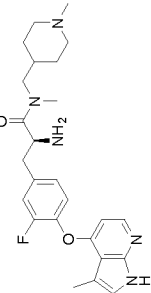
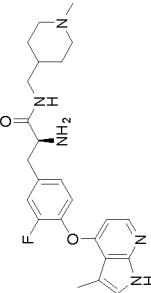
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
23	 (S)-4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)-N,N-dimethylpiperazine-1-carboxamide	1E-a / N,N-dimethyl-piperazine-1-carboxamide	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.33 (dd, J=1.9, 11.9 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.14-7.10 (m, 2H), 6.14 (d, J=5.3 Hz, 1H), 3.95 (dd, J=6.8, 6.8 Hz, 1H), 3.55-3.35 (m, 4H), 3.12-3.06 (m, 2H), 3.01-2.78 (m, 3H), 2.74 (s, 6H), 2.68 (dd, J=7.4, 13.3 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 1.74 (s, 2H).	Rt = 2.28 min, m/z 469.1 [M+H] ⁺ (Method 1)
24	 (S)-2-amino-1-((1S,4S)-5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(3-fluoro-4-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)propan-1-one	1E-a / (1S,4S)-2-benzyl-2,5-diazabicyclo[2.2.1]heptane	¹ H NMR (400 MHz, d6-DMSO) δ 11.38 (d, J=0.6 Hz, 1H), 8.00-7.91 (m, 1H), 7.38-7.11 (m, 9H), 6.14 (dd, J=3.4, 5.0 Hz, 1H), 4.50-4.38 (m, 1H), 3.74-3.56 (m, 2H), 3.50-3.34 (m, 3H), 3.23-3.04 (m, 1H), 2.86-2.68 (m, 3H), 2.39-2.28 (m, 3H), 1.81-1.75 (m, 2H), 1.50-1.38 (m, 1H).	Rt = 2.00 min, m/z 500.1 [M+H] ⁺ (Method 1)
25	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one	1E-a / (1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptane	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.99 (dd, J=3.5, 5.4 Hz, 1H), 7.35-7.20 (m, 2H), 7.15-7.09 (m, 2H), 6.25-6.15 (m, 1H), 4.44-4.35 (m, 1H), 3.70-3.60 (m, 1H), 3.37-3.33 (m, 2H), 3.15-2.98 (m, 1H), 2.80-2.66 (m, 3H), 2.38 (s, 3H), 2.27 (s, 1H), 2.13 (s, 2H), 1.76-1.69 (m, 2H), 1.44-1.35 (m, 1H).	Rt = 1.66 min, m/z 424.0 [M+H] ⁺ (Method 1)

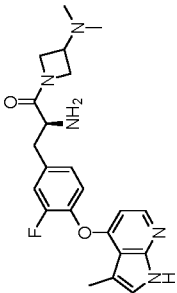
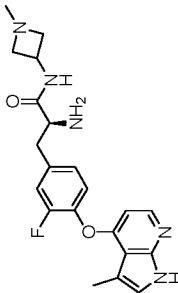
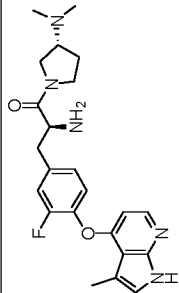
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
26	 (S)-2-amino-1-((3S,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / (2R,6S)-1-benzyl-2,6-dimethylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.41 (s, 1H), 7.98 (dd, J=5.5, 7.8 Hz, 1H), 7.37-7.08 (m, 9H), 6.17 (dd, J=5.5, 10.0 Hz, 1H), 4.18-4.15 (m, 1H), 3.99 (q, J=6.3 Hz, 1H), 3.81-3.55 (m, 3H), 2.84-2.54 (m, 3H), 2.43-2.38 (m, 4H), 2.25-2.20 (m, 1H), 1.86-1.80 (m, 1H), 0.98-0.86 (m, 6H).	Rt = 2.26 min, m/z 516.1 [M+H] ⁺ (Method 1)
27	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one (ee% n.d.)	1E-a / 1-(pyrimidin-2-ylmethyl)piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.50-8.48 (m, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.76 (dt, J=1.8, 7.7 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.34-7.21 (m, 3H), 7.17-7.13 (m, 1H), 7.11 (d, J=8.7 Hz, 1H), 6.18 (d, J=5.4 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.57 (s, 2H), 3.56-3.38 (m, 4H), 2.80 (dd, J=6.4, 13.2 Hz, 1H), 2.68 (dd, J=7.3, 13.1 Hz, 1H), 2.41-2.36 (m, 5H), 2.27-2.22 (m, 1H), 2.12-2.07 (m, 1H), 1.90-1.88 (m, 2H).	Rt = 1.90 min, m/z 489.3 [M+H] ⁺ (Method 1)
28	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-ylmethyl)piperazin-1-yl)propan-1-one	1E-a / 1-(pyridin-3-ylmethyl)piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.47 (dd, J=1.7, 4.7 Hz, 2H), 7.98 (d, J=5.4 Hz, 1H), 7.69 (td, J=1.9, 7.8 Hz, 1H), 7.36 (dd, J=4.8, 7.8 Hz, 1H), 7.31 (dd, J=2.0, 12.0 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.16-7.13 (m, 1H), 7.10 (d, J=8.2 Hz, 1H), 6.16 (d, J=5.0 Hz, 1H), 3.93 (t, J=6.9 Hz, 1H), 3.50-3.45 (m, 7H), 2.80 (dd, J=6.4, 13.2 Hz, 1H), 2.67 (dd, J=7.3, 13.3 Hz, 1H), 2.39 (d, J=0.9 Hz, 3H), 2.37-2.30 (m, 2H), 2.25-2.16 (m, 1H), 2.10-2.04 (m, 1H), 1.87 (s, 1H).	Rt = 1.89 min, m/z 489.2 [M+H] ⁺ (Method 1)

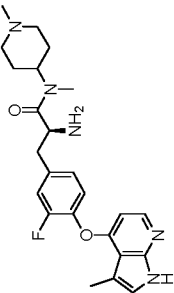
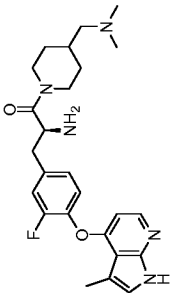
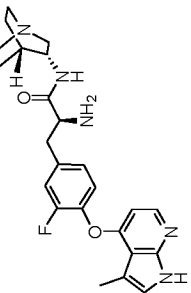
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
29	 (ee% n.d.) (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one	1E-a / tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate	¹ H NMR (400 MHz, DMSO) δ 11.41 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.31-7.21 (m, 2H), 7.14 (s, 1H), 7.08 (d, J=7.2 Hz, 1H), 6.15 (d, J=5.1 Hz, 1H), 4.14 (d, J=9.0 Hz, 1H), 3.87 (d, J=10.1 Hz, 1H), 3.83-3.77 (m, 1H), 3.64 (d, J=9.1 Hz, 1H), 3.38 (t, J=6.7 Hz, 2H), 3.20-3.10 (m, 2H), 3.03 (d, J=7.6 Hz, 1H), 2.88 (s, 1H), 2.77-2.63 (m, 2H), 2.37 (s, 3H), 1.69 (s, 2H).	Rt = 1.63 min, m/z 410.1 [M+H] ⁺ (Method 1)
30	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)propan-1-one	1E-a / (3aR,6aS)-2-methyloctahydropyrrolo[3,4-c]pyrrole	¹ H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.98 (dd, J=1.2, 5.4 Hz, 1H), 7.30 (ddd, J=1.8, 5.0, 11.9 Hz, 1H), 7.27-7.20 (m, 1H), 7.15-7.09 (m, 2H), 6.14 (dd, J=3.1, 5.2 Hz, 1H), 3.75-3.65 (m, 2H), 3.57-3.39 (m, 2H), 3.27-3.03 (m, 2H), 2.85-2.59 (m, 3H), 2.47-2.38 (m, 6H), 2.23-2.09 (m, 4H), 1.78 (s, 2H).	Rt = 1.69 min, m/z 438.1 [M+H] ⁺ (Method 1)
31	 (ee% n.d.) (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-yl)propan-1-one	1E-a / tert-butyl (3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate	¹ H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 8.01-7.97 (m, 1H), 7.35-7.27 (m, 1H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.08 (m, 2H), 6.20-6.11 (m, 1H), 3.80-3.55 (m, 2H), 3.53-3.43 (m, 1H), 3.19 (dd, J=4.1, 12.2 Hz, 3H), 3.11-2.95 (m, 2H), 2.89-2.78 (m, 3H), 2.75-2.56 (m, 4H), 2.46-2.41 (m, 1H), 2.38 (s, 3H).	Rt = 1.71 min, m/z 424.1 [M+H] ⁺ (Method 1)

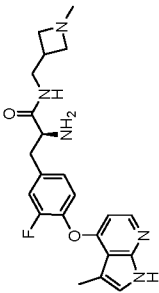
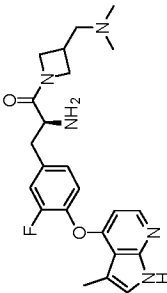
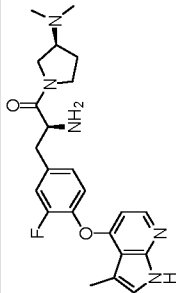
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
32	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(hydroxymethyl)cyclohexyl)propanamide	1E-a / (1-aminocyclohexyl)methanol	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.35-7.21 (m, 3H), 7.15-7.11 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 4.71 (t, J=5.8 Hz, 1H), 3.48 (dd, J=5.1, 7.9 Hz, 1H), 3.43 (d, J=5.8 Hz, 2H), 2.95 (dd, J=5.3, 13.4 Hz, 1H), 2.70 (dd, J=7.8, 13.2 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.01-1.90 (m, 2H), 1.46-1.39 (m, 3H), 1.34-1.14 (m, 6H).	Rt = 2.51 min, m/z 441.3 [M+H] ⁺ (Method 1)
33	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)propanamide	1E-a / (4-aminotetrahydro-2H-pyran-4-yl)methanol	¹ H NMR (400 MHz, DMSO) δ 11.38-11.38 (m, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.42 (s, 1H), 7.32 (dd, J=1.9, 11.9 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.11 (m, 2H), 6.17 (d, J=5.3 Hz, 1H), 4.74 (dd, J=5.9, 5.9 Hz, 1H), 3.64-3.55 (m, 2H), 3.50-3.36 (m, 4H), 3.29 (dd, J=2.5, 11.1 Hz, 1H), 2.93 (dd, J=5.7, 13.5 Hz, 1H), 2.70 (dd, J=7.8, 13.5 Hz, 1H), 2.39 (s, 3H), 1.99-1.88 (m, 4H), 1.59-1.48 (m, 2H).	Rt = 2.09 min, m/z 443.4 [M+H] ⁺ (Method 3)
34	 (S)-2-amino-N-(1-cyanocyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (ec% = 56%)	1E-a / 1-aminocyclohexane-1-carbonitrile	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.29 (dd, J=2.5, 12.0 Hz, 1H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.09 (m, 2H), 6.16 (d, J=5.3 Hz, 1H), 3.47 (t, J=7.2 Hz, 1H), 2.89 (dd, J=6.1, 13.3 Hz, 1H), 2.77-2.66 (m, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.16-2.12 (m, 2H), 1.84 (s, 2H), 1.66-1.22 (m, 9H).	Rt = 2.59 min, m/z 436.4 [M+H] ⁺ (Method 3)

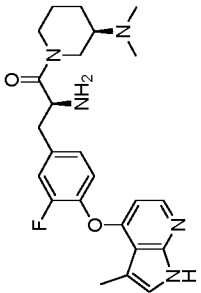
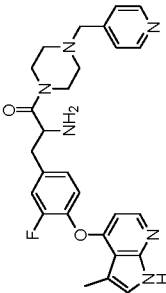
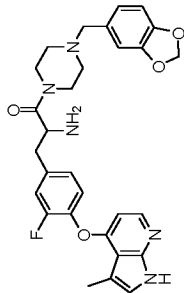
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
35	 (S)-1-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamido)cyclohexanecarboxamide	1E-a / 1-amido-cyclohexane-1-carboxamide	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.5 Hz, 1H), 7.67 (s, 1H), 7.33 (dd, J=1.8, 12.2 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.13 (m, 2H), 6.92 (s, 1H), 6.79 (s, 1H), 6.17 (d, J=5.3 Hz, 1H), 3.53 (dd, J=5.7, 7.8 Hz, 1H), 2.97 (dd, J=5.4, 13.5 Hz, 1H), 2.73-2.66 (m, 1H), 2.38 (s, 3H), 2.07-1.92 (m, 4H), 1.64-1.56 (m, 2H), 1.48-1.29 (m, 4H), 1.18-1.12 (m, 2H).	Rt = 2.40 min, m/z 454.4 [M+H] ⁺ (Method 3)
36	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(2-hydroxyethyl)cyclohexyl)propanamide	1E-a / 2-(1-aminocyclohexyl)ethan-1-ol	¹ H NMR (400 MHz, DMSO) δ 11.36 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.33 (dd, J=1.8, 11.6 Hz, 1H), 7.28-7.21 (m, 2H), 7.16-7.13 (m, 2H), 6.17 (d, J=5.3 Hz, 1H), 4.22 (dd, J=5.1, 5.1 Hz, 1H), 3.40 (dd, J=7.3, 12.3 Hz, 3H), 2.95 (dd, J=5.3, 13.3 Hz, 1H), 2.69-2.63 (m, 1H), 2.39 (s, 3H), 2.08-2.01 (m, 2H), 1.88-1.77 (m, 4H), 1.45-1.33 (m, 3H), 1.27-1.21 (m, 5H).	Rt = 2.59 min, m/z 455.5 [M+H] ⁺ (Method 3)
37	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)-1-methylpiperidin-4-yl)propanamide	1E-a / (4-amino-1-methylpiperidin-4-yl)methanol	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.32 (dd, J=2.0, 12.2 Hz, 1H), 7.29-7.21 (m, 2H), 7.15-7.11 (m, 2H), 6.17 (d, J=5.2 Hz, 1H), 4.71 (dd, J=5.9, 5.9 Hz, 1H), 3.49-3.41 (m, 3H), 2.93 (dd, J=5.6, 13.5 Hz, 1H), 2.74-2.66 (m, 1H), 2.43-2.38 (m, 5H), 2.08 (s, 3H), 2.01-1.79 (m, 6H), 1.53-1.43 (m, 2H).	Rt = 3.03 min, m/z 456.3 [M+H] ⁺ (Method 2)

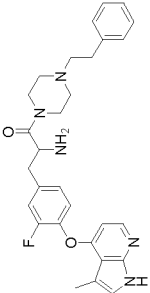
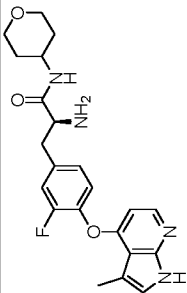
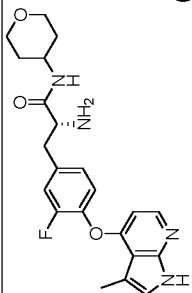
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
38	 (S)-2-amino-N-(1-((dimethylamino)methyl)cyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-a / 1-((dimethylamino)-methyl)-cyclohexan-1-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.36-7.31 (m, 2H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.13 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 3.44 (dd, J=5.6, 7.7 Hz, 1H), 2.95 (dd, J=5.4, 13.4 Hz, 1H), 2.69-2.62 (m, 1H), 2.47-2.39 (m, 2H), 2.38 (s, 3H), 2.18 (s, 6H), 2.06-2.01 (m, 2H), 1.80-1.80 (m, 2H), 1.47-1.12 (m, 8H).	Rt = 2.11 min, m/z 468.4 [M+H] ⁺ (Method 1)
39	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)methyl)propanamide	1E-a / N-methyl-1-(1-methylpiperidin-4-yl)methanamine	¹ H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 7.99-7.96 (m, 1H), 7.26-7.19 (m, 1H), 7.13-7.07 (m, 2H), 6.12 (d, J=5.4 Hz, 1H), 3.94-3.75 (m, 1H), 3.37 (dd, J=7.5, 12.9 Hz, 2H), 3.21-2.98 (m, 1H), 2.93 (s, 2H), 2.91-2.79 (m, 2H), 2.78 (s, 1H), 2.68 (dd, J=6.7, 13.0 Hz, 3H), 2.38 (s, 3H), 2.09 (d, J=5.4 Hz, 3H), 1.75-1.66 (m, 3H), 1.47-1.31 (m, 3H), 1.15-0.96 (m, 2H).	Rt = 1.78 min, m/z 454.2 [M+H] ⁺ (Method 1)
40	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylpiperidin-4-yl)methyl)propanamide	1E-a / (1-methylpiperidin-4-yl)methanamine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.5 Hz, 1H), 7.80 (dd, J=6.0, 6.0 Hz, 1H), 7.28-7.20 (m, 2H), 7.14 (d, J=0.9 Hz, 1H), 7.08 (dd, J=1.4, 8.1 Hz, 1H), 6.14 (d, J=5.7 Hz, 1H), 3.41 (dd, J=6.6, 6.6 Hz, 1H), 3.00-2.65 (m, 7H), 2.39 (d, J=0.9 Hz, 3H), 2.08 (s, 3H), 1.74-1.68 (m, 3H), 1.44-1.44 (m, 2H), 1.23-1.18 (m, 1H), 1.07-0.97 (m, 2H).	Rt = 1.69 min, m/z 440.2 [M+H] ⁺ (Method 1)

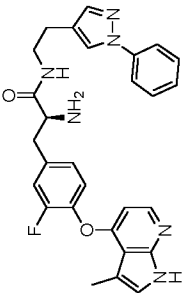
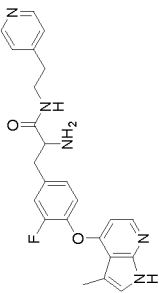
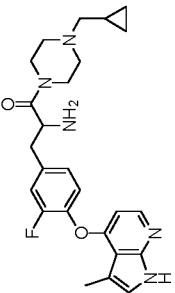
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
41	 (S)-2-amino-1-(3-(dimethylamino)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / N,N-dimethylazetidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (dd, J=2.2, 5.4 Hz, 1H), 7.33-7.22 (m, 2H), 7.15-7.09 (m, 2H), 6.17 (dd, J=5.3, 14.4 Hz, 1H), 4.15-3.94 (m, 1H), 3.86-3.42 (m, 4H), 3.04-2.85 (m, 1H), 2.81-2.63 (m, 2H), 2.39 (s, 3H), 2.04 (d, J=10.4 Hz, 6H), 1.71 (s, 2H).	Rt = 1.59 min, m/z 412.2 [M+H] ⁺ (Method 1)
42	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylazetidin-3-yl)propanamide	1E-a / 1-methylazetidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.15 (d, J=7.7 Hz, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.27-7.20 (m, 2H), 7.13 (s, 1H), 7.07 (d, J=7.8 Hz, 1H), 6.18 (d, J=5.3 Hz, 1H), 4.22-4.17 (m, 1H), 3.44 (dd, J=6.7, 14.1 Hz, 2H), 3.36 (t, J=6.9 Hz, 1H), 2.86 (dd, J=5.9, 13.3 Hz, 1H), 2.78-2.66 (m, 3H), 2.38 (s, 3H), 2.18 (s, 3H), 1.81 (s, 2H).	Rt = 1.60 min, m/z 398.1 [M+H] ⁺ (Method 1)
43	 (S)-2-amino-1-((R)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / (R)-N,N-dimethylpyrrolidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (dd, J=2.3, 5.4 Hz, 1H), 7.34-7.21 (m, 2H), 7.15-7.09 (m, 2H), 6.15 (dd, J=5.5, 8.6 Hz, 1H), 3.71-3.41 (m, 3H), 3.18-3.08 (m, 1H), 2.94-2.67 (m, 3H), 2.60-2.52 (m, 1H), 2.39 (d, J=1.6 Hz, 3H), 2.11 (d, J=3.4 Hz, 6H), 2.05-1.91 (m, 1H), 1.76-1.74 (m, 2H), 1.60-1.50 (m, 1H).	Rt = 1.61 min, m/z 426.2 [M+H] ⁺ (Method 1)

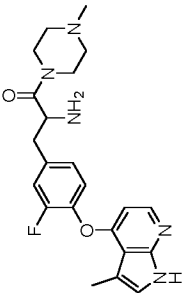
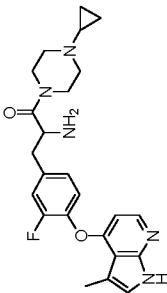
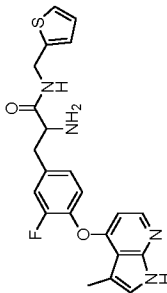
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
44	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-1H-(1-methylpiperidin-4-yl)propanamide	1E-a / N,1-dimethyl-1-piperidin-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.00-7.97 (m, 1H), 7.33-7.27 (m, 1H), 7.25-7.19 (m, 1H), 7.15-7.08 (m, 2H), 6.15-6.11 (m, 1H), 4.25-3.50 (m, 2H), 2.82-2.67 (m, 6H), 2.37 (s, 3H), 2.13 (d, J=1.8 Hz, 3H), 1.97-1.81 (m, 3H), 1.76-1.54 (m, 4H), 1.39-1.02 (m, 2H).	Rt = 1.72 min, m/z 440.2 [M+H] ⁺ (Method 1)
45	 (S)-2-amino-1-(4-((dimethylamino)methyl)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / N,N-dimethyl-1-(piperidin-4-yl)methanamine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.33-7.21 (m, 2H), 7.14 (s, 1H), 7.10 (d, J=8.3 Hz, 1H), 6.14 (d, J=5.5 Hz, 1H), 4.37 (t, J=15.2 Hz, 1H), 3.97-3.84 (m, 2H), 2.96-2.60 (m, 3H), 2.38 (s, 3H), 2.08 (d, J=16.4 Hz, 6H), 2.03 (d, J=6.8 Hz, 1H), 1.91 (d, J=6.7 Hz, 1H), 1.75-1.56 (m, 5H), 1.09-0.29 (m, 3H).	Rt = 1.80 min, m/z 454.2 [M+H] ⁺ (Method 1)
46	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((R)-quinuclidin-3-yl)propanamide	1E-a / (3R)-quinuclidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.79 (d, J=7.2 Hz, 1H), 7.27-7.19 (m, 2H), 7.14 (s, 1H), 7.07 (dd, J=1.4, 8.3 Hz, 1H), 6.15 (d, J=5.3 Hz, 1H), 3.69 (d, J=7.0 Hz, 1H), 3.44 (t, J=7.1 Hz, 1H), 3.05-2.98 (m, 1H), 2.84 (dd, J=6.9, 13.2 Hz, 1H), 2.76-2.62 (m, 5H), 2.40-2.32 (m, 5H), 1.58-1.43 (m, 4H), 1.24-1.16 (m, 2H).	Rt = 1.84 min, m/z 438.2 [M+H] ⁺ (Method 1)

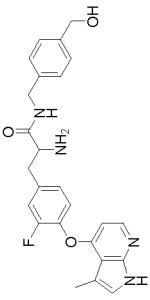
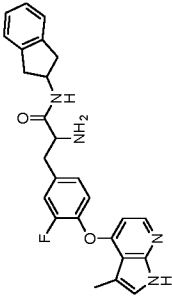
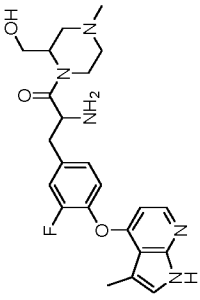
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
47	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylazetidin-3-yl)methyl)propanamide	1E-a / (1-methylazetidin-3-yl)-methanamine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.90 (dd, J=5.7, 5.7 Hz, 1H), 7.28-7.20 (m, 2H), 7.14 (s, 1H), 7.08 (dd, J=1.3, 8.2 Hz, 1H), 6.17 (d, J=5.4 Hz, 1H), 3.42-3.06 (m, 6H), 2.93-2.69 (m, 5H), 2.39-2.30 (m, 4H), 2.13 (s, 3H).	Rt = 1.70 min, m/z 412.2 [M+H] ⁺ (Method 1)
48	 (S)-2-amino-1-(3-((dimethylamino)methyl)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / 3-(azetidin-3-yl)-N,N-dimethylmethanamine	¹ H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.33-7.23 (m, 2H), 7.15-7.09 (m, 2H), 6.14 (dd, J=2.5, 5.4 Hz, 1H), 4.15-3.41 (m, 4H), 3.30-3.11 (m, 1H), 2.80-2.58 (m, 3H), 2.43-2.35 (s, 4H), 2.22-2.13 (m, 1H), 2.08 (d, J=18.4 Hz, 6H), 1.76-1.76 (m, 2H).	Rt = 1.68 min, m/z 426.2 [M+H] ⁺ (Method 1)
49	 (S)-2-amino-1-((S)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / (S)-N,N-dimethylpyrrolidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (d, J=6.0 Hz, 1H), 7.98 (dd, J=5.4, 10.4 Hz, 1H), 7.31-7.21 (m, 2H), 7.15-7.08 (m, 2H), 6.21-6.10 (m, 1H), 3.80-3.63 (m, 2H), 3.56-3.40 (m, 1H), 3.23-2.92 (m, 2H), 2.81-2.59 (m, 3H), 2.44-2.31 (m, 4H), 2.12 (d, J=2.3 Hz, 6H), 2.01-1.98 (m, 1H), 1.72-1.39 (m, 2H).	Rt = 1.69 min, m/z 426.2 [M+H] ⁺ (Method 1)

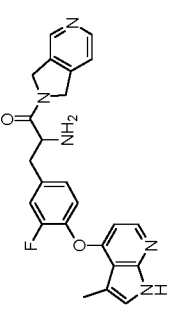
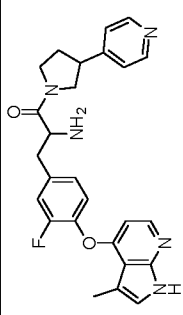
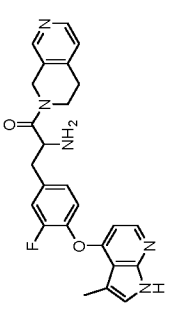
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
50	 (S)-2-amino-1-((R)-3-(dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-a / (R)-N,N-dimethyl-piperidin-3-amine	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.98 (dd, J=5.0, 5.0 Hz, 1H), 7.36-7.07 (m, 4H), 6.14 (dd, J=6.2, 6.2 Hz, 1H), 4.36-4.16 (m, 1H), 3.99-3.72 (m, 2H), 2.92-2.61 (m, 4H), 2.38 (d, J=3.2 Hz, 3H), 2.17 (d, J=20.3 Hz, 6H), 1.80-1.63 (m, 4H), 1.46-0.98 (m, 3H).	Rt = 1.78 min, m/z 440.2 [M+H] ⁺ (Method 1)
51	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-ylmethyl)piperazin-1-yl)propan-1-one	1E-b / 1-(pyridin-4-ylmethyl)-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 8.52-8.50 (m, 2H), 7.98 (d, J=5.5 Hz, 1H), 7.34-7.28 (m, 3H), 7.24 (t, J=8.4 Hz, 1H), 7.15-7.09 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.51-3.47 (m, 6H), 2.80 (dd, J=6.4, 13.1 Hz, 1H), 2.67 (dd, J=7.3, 13.2 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.38-2.33 (m, 2H), 2.23-2.18 (m, 1H), 2.11-2.03 (m, 1H), 1.78-1.74 (m, 2H).	Rt = 1.86 min, m/z 489.3 [M+H] ⁺ (Method 1)
52	 2-amino-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-b / 1-(benzo[d][1,3]dioxol-5-ylmethyl)-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.31 (dd, J=2.1, 11.9 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.16-7.12 (m, 1H), 7.10 (dd, J=1.3, 8.3 Hz, 1H), 6.84 (dd, J=3.1, 4.7 Hz, 2H), 6.72 (dd, J=1.5, 7.9 Hz, 1H), 6.16 (d, J=5.4 Hz, 1H), 5.98 (s, 2H), 3.93 (t, J=6.8 Hz, 1H), 3.36-3.33 (m, 6H), 2.79 (dd, J=6.4, 13.1 Hz, 1H), 2.68 (dd, J=6.8, 12.9 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.36-2.26 (m, 2H), 2.21-2.12 (m, 1H), 2.05-1.96 (m, 1H), 1.77 (s, 2H).	Rt = 2.09 min, m/z 532.4 [M+H] ⁺ (Method 1)

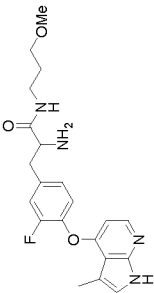
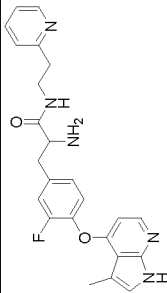
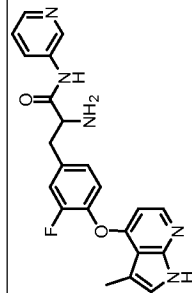
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
53	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenethylpiperazin-1-yl)propan-1-one	1E-b / 1-phenethylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.96 (d, J=5.4 Hz, 1H), 7.33-7.09 (m, 9H), 6.15 (d, J=4.8 Hz, 1H), 3.96 (t, J=6.9 Hz, 1H), 3.59-3.51 (m, 1H), 3.42-3.36 (m, 3H), 2.80 (dd, J=6.8, 13.1 Hz, 1H), 2.75-2.65 (m, 3H), 2.49-2.39 (m, 4H), 2.34 (d, J=1.0 Hz, 3H), 2.27-2.17 (m, 1H), 2.09-1.98 (m, 1H), 1.76 (s, 2H).	Rt = 2.17 min, m/z 502.3 [M+H] ⁺ (Method 1)
54	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide	1E-a / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.76 (d, J=7.8 Hz, 1H), 7.29-7.20 (m, 2H), 7.16-7.12 (m, 1H), 7.11-7.06 (m, 1H), 6.16 (d, J=4.8 Hz, 1H), 3.83-3.71 (m, 3H), 3.43-3.37 (m, 1H), 3.37-3.35 (m, 1H), 2.88 (dd, J=6.0, 13.2 Hz, 1H), 2.73 (dd, J=7.5, 13.1 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.17 (s, 2H), 1.66-1.56 (m, 2H), 1.44-1.22 (m, 3H).	Rt = 2.20 min, m/z 413.0 [M+H] ⁺ (Method 1)
55	 (R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide (Separated by chiral HPLC Method A)	1E-b / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.29-7.20 (m, 2H), 7.16-7.12 (m, 1H), 7.11-7.06 (m, 1H), 6.16 (d, J=5.4 Hz, 1H), 3.83-3.70 (m, 3H), 3.44-3.35 (m, 2H), 2.88 (dd, J=6.0, 13.2 Hz, 1H), 2.72 (dd, J=7.5, 13.3 Hz, 1H), 2.38 (d, J=1.1 Hz, 3H), 2.09 (s, 2H), 1.66-1.56 (m, 2H), 1.44-1.22 (m, 3H).	Rt = 2.17 min, m/z 413.2 [M+H] ⁺ (Method 1)

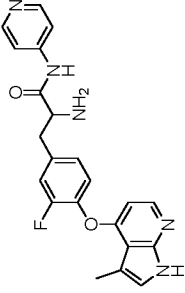
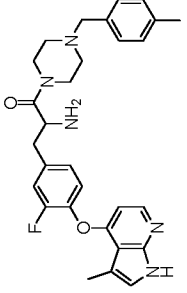
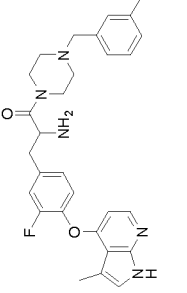
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
56	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(1-phenyl-1H-pyrazol-4-yl)ethyl)propanamide	1E-a / 2-(1-phenyl-1H-pyrazol-4-yl)ethan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.30 (s, 1H), 8.02 (t, J=5.8 Hz, 1H), 7.96 (d, J=5.5 Hz, 1H), 7.81-7.76 (m, 2H), 7.59 (s, 1H), 7.49-7.44 (m, 2H), 7.31-7.20 (m, 3H), 7.16-7.12 (m, 1H), 7.09 (d, J=8.1 Hz, 1H), 6.15 (d, J=4.8 Hz, 1H), 3.41 (dd, J=5.3, 7.9 Hz, 1H), 3.31-3.25 (m, 2H), 2.94 (dd, J=5.2, 13.4 Hz, 1H), 2.69 (dd, J=8.0, 13.5 Hz, 1H), 2.61 (t, J=7.2 Hz, 2H), 2.37 (d, J=1.0 Hz, 3H), 1.81 (s, 2H).	Rt = 2.70 min, m/z 499.3 [M+H] ⁺ (Method 1)
57	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide	1E-b / 2-(pyridin-4-yl)ethan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.46-8.44 (m, 2H), 8.01-7.93 (m, 2H), 7.29-7.19 (m, 4H), 7.14-7.05 (m, 2H), 6.16 (d, J=4.8 Hz, 1H), 3.41-3.36 (m, 3H), 2.90 (dd, J=5.3, 13.3 Hz, 1H), 2.70 (t, J=7.3 Hz, 2H), 2.65 (dd, J=8.2, 13.2 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 1.96 (s, 2H).	Rt = 1.81 min, m/z 434.0 [M+H] ⁺ (Method 1)
58	 2-amino-1-(4-(cyclopropylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-b / 1-(cyclopropyl-methyl)-piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.31 (dd, J=1.9, 11.7 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.15-7.08 (m, 2H), 6.15 (d, J=5.6 Hz, 1H), 3.96 (t, J=7.0 Hz, 1H), 3.59-3.54 (m, 1H), 3.44-3.37 (m, 2H), 3.36-3.29 (m, 1H), 2.79 (dd, J=6.8, 13.1 Hz, 1H), 2.70 (dd, J=6.9, 12.9 Hz, 1H), 2.47-2.39 (m, 2H), 2.38 (d, J=1.0 Hz, 3H), 2.19-2.10 (m, 3H), 1.98-1.93 (m, 1H), 1.73 (s, 2H), 0.84-0.75 (m, 1H), 0.48-0.42 (m, 2H), 0.07-0.01 (m, 2H).	Rt = 1.78 min, m/z 452.3 [M+H] ⁺ (Method 1)

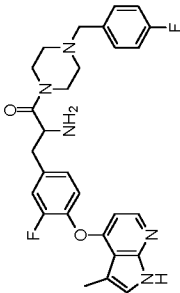
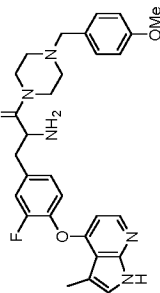
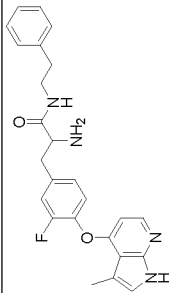
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
59	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one	1E-b / 1-methylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.99-7.97 (m, 1H), 7.31 (dd, J=2.0, 11.9 Hz, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.15-7.08 (m, 2H), 6.16 (d, J=4.8 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.54-3.44 (m, 1H), 3.43-3.34 (m, 3H), 2.79 (dd, J=6.6, 13.1 Hz, 1H), 2.69 (dd, J=7.1, 13.1 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.33-2.23 (m, 2H), 2.13 (s, 3H), 2.11-2.04 (m, 1H), 1.94-1.89 (m, 1H), 1.75-1.72 (m, 2H).	Rt = 1.60 min, m/z 412.2 [M+H] ⁺ (Method 1)
60	 2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-b / 1-cyclopropylpiperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.5 Hz, 1H), 7.31 (dd, J=2.0, 11.6 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.14-7.09 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.52-3.45 (m, 1H), 3.41-3.24 (m, 5H), 2.80 (dd, J=6.8, 13.1 Hz, 1H), 2.70 (dd, J=7.1, 13.2 Hz, 1H), 2.37 (d, J=1.0 Hz, 3H), 2.34-2.28 (m, 1H), 2.14-2.10 (m, 1H), 1.73 (s, 2H), 1.57-1.50 (m, 1H), 0.44-0.37 (m, 2H), 0.31 (m, 2H).	Rt = 1.87 min, m/z 438.3 [M+H] ⁺ (Method 1)
61	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(thiophen-2-ylmethyl)propanamide	1E-b / thiophen-2-ylmethanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (br. s., 1H), 8.52 (br. s., 1H), 8.16 (s, 1H), 7.98 (d, J=5.5 Hz, 1H), 7.02-7.41 (m, 5H), 6.93 (d, J=3.5 Hz, 2H), 6.16 (d, J=5.1 Hz, 1H), 4.45 (dd, J=8.2, 5.9 Hz, 2H), 3.44-3.67 (m, 1H), 2.97 (m, 1H), 2.75 (dd, J=13.5, 8.0 Hz, 1H), 2.39 (s, 3H).	Rt = 2.46 min, m/z 425.1 [M+H] ⁺ (Method 1)

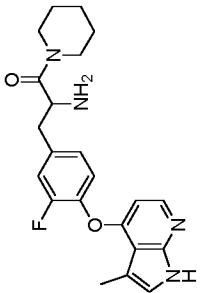
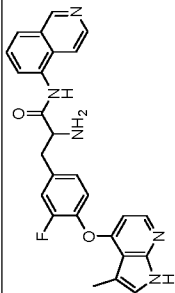
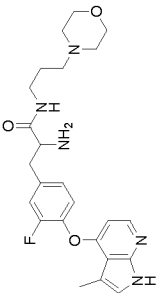
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
62	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)benzyl)propanamide	1E-b / (4-(aminomethyl)-phenyl)-methanol	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.36-8.26 (m, 1H), 7.97 (d, J=5.4Hz, 1H), 7.31-7.20 (m, 4H), 7.15-7.07 (m, 4H), 6.16 (d, J=5.4Hz, 1H), 5.11-5.11 (m, 1H), 4.44 (s, 2H), 4.32-4.18 (m, 2H), 3.49 (dd, J=5.7, 13.3Hz, 1H), 2.74 (dd, J=8.1, 13.1Hz, 1H), 2.40 (d, J=1.0Hz, 3H).	Rt = 2.18 min, m/z 449.2 [M+H] ⁺ (Method 1)
63	 2-amino-N-(2,3-dihydro-1H-inden-2-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-b / 2,3-dihydro-1H-inden-2-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (br. s., 1H), 8.21 (d, J=7.0Hz, 1H), 8.15 (s, 1H), 7.95 (d, J=5.7Hz, 1H), 6.97-7.33 (m, 8H), 6.16 (d, J=5.7Hz, 1H), 4.34-4.63 (m, 1H), 3.55 (m, 1H), 3.15 (m, 2H), 2.78 (m, 4H), 2.39 (s, 3H).	Rt = 2.71 min, m/z 445.2 [M+H] ⁺ (Method 1)
64	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-(hydroxymethyl)-4-methylpiperazin-1-yl)propan-1-one	1E-b / (4-methylpiperazin-2-yl)-methanol	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.50 (br. s., 1H), 10.07 - 11.04 (m, 1H), 8.32 (br. s., 3H), 8.03 (d, J=5.3 Hz, 1H), 7.03 - 7.61 (m, 4H), 6.28 (m, 1H), 2.64 - 4.92 (m, 15 H), 2.39 (br. s., 3 H).	Rt = 1.58 min, m/z 442.3 [M+H] ⁺ (Method 1)

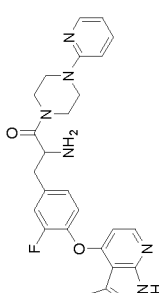
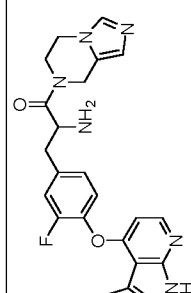
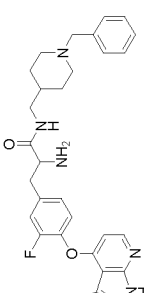
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
65	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)propan-1-one	1E-b / 2,3-dihydro-1H-pyrrolo[3,4-c]pyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.59 (d, J=9.9 Hz, 1H), 8.50 (d, J=5.0 Hz, 1H), 7.83 (d, J=5.4 Hz, 1H), 7.44-7.35 (m, 2H), 7.27-7.15 (m, 2H), 7.12 (s, 1H), 5.95 (d, J=5.1 Hz, 1H), 5.07-5.01 (m, 1H), 4.78-4.59 (m, 3H), 3.81-3.75 (m, 1H), 2.91 (dd, J=6.2, 13.2 Hz, 1H), 2.74 (dd, J=7.9, 13.3 Hz, 1H), 2.35 (d, J=1.0 Hz, 3H), 1.83 (s, 2H).	Rt = 1.96 min, m/z 432.2 [M+H] ⁺ (Method 1)
66	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(pyridin-4-yl)pyrrolidin-1-yl)propan-1-one	1E-b / rac-4-(pyrrolidin-3-yl)pyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.53-8.49 (m, 1H), 8.48-8.42 (m, 1H), 7.99-7.90 (m, 1H), 7.75-7.55 (m, 1H), 7.39-7.12 (m, 5H), 6.16-6.08 (m, 1H), 3.93-3.37 (m, 4H), 3.29-3.10 (m, 2H), 2.90-2.81 (m, 1H), 2.74-2.66 (m, 1H), 2.38-2.36 (m, 3H), 2.32-2.18 (m, 1H), 2.08-1.65 (m, 3H).	Rt = 1.97 min, m/z 460.3 [M+H] ⁺ (Method 1)
67	 2-amino-1-(3,4-dihydro-2,7-naphthyridin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-b / 1,2,3,4-tetrahydro-2,7-naphthyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.44-8.28 (m, 2H), 7.95-7.91 (m, 1H), 7.36-7.25 (m, 1H), 7.19-7.07 (m, 4H), 6.10-6.01 (m, 1H), 4.80-4.58 (m, 2H), 4.13-3.99 (m, 1H), 3.86-3.73 (m, 1H), 3.69-3.50 (m, 1H), 2.92-2.62 (m, 4H), 2.37 (d, J=2.4 Hz, 3H), 1.85 (s, 2H).	Rt = 1.82 min, m/z 446.2 [M+H] ⁺ (Method 1)

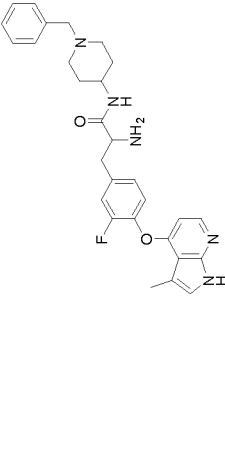
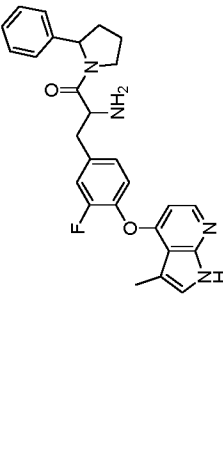
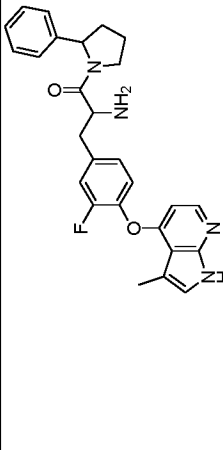
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
68	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-methoxypropyl)propanamide	1E-b / 3-methoxypropan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.85 (t, J=5.7 Hz, 1H), 7.29-7.21 (m, 2H), 7.14-7.07 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 3.42-3.37 (m, 1H), 3.24 (t, J=6.3 Hz, 2H), 3.20 (s, 3H), 3.18-3.02 (m, 4H), 2.91 (dd, J=5.7, 13.3 Hz, 1H), 2.71 (dd, J=7.6, 13.3 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 1.62-1.53 (m, 2H).	Rt = 2.21 min, m/z 401.2 [M+H] ⁺ (Method 1)
69	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-2-yl)ethyl)propanamide	1E-b / 2-(pyridin-2-yl)ethan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.49 (dd, J=2.1, 5.3 Hz, 1H), 8.05 (t, J=5.7 Hz, 1H), 7.95 (d, J=5.4 Hz, 1H), 7.69 (dt, J=1.9, 7.7 Hz, 1H), 7.30-7.19 (m, 4H), 7.14-7.06 (m, 2H), 6.16 (dd, J=0.8, 5.4 Hz, 1H), 3.48-3.37 (m, 3H), 2.93 (dd, J=5.3, 13.4 Hz, 1H), 2.83 (t, J=7.3 Hz, 2H), 2.70 (dd, J=8.1, 13.7 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H).	Rt = 1.92 min, m/z 434.2 [M+H] ⁺ (Method 1)
70	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-3-yl)propanamide	1E-b / pyridin-3-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.76-8.75 (m, 1H), 8.26 (dd, J=1.5, 4.7 Hz, 1H), 8.08-8.04 (m, 1H), 7.94 (d, J=5.4 Hz, 1H), 7.36-7.31 (m, 2H), 7.23 (t, J=8.4 Hz, 1H), 7.16-7.12 (m, 2H), 6.08 (d, J=4.8 Hz, 1H), 3.63 (dd, J=5.7, 7.9 Hz, 1H), 3.03 (dd, J=5.6, 13.4 Hz, 1H), 2.82 (dd, J=8.0, 13.4 Hz, 1H), 2.37 (d, J=1.0 Hz, 3H).	Rt = 2.05 min, m/z 406.2 [M+H] ⁺ (Method 1)

Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
71	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-4-yl)propanamide	1E-b / pyridin-4-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 8.44-8.41 (m, 2H), 7.94 (d, J=5.5 Hz, 1H), 7.62-7.59 (m, 2H), 7.34 (dd, J=1.8, 11.9 Hz, 1H), 7.23 (t, J=8.4 Hz, 1H), 7.15-7.11 (m, 2H), 6.07 (d, J=4.8 Hz, 1H), 3.63 (dd, J=5.7, 8.0 Hz, 1H), 3.01 (dd, J=5.6, 13.4 Hz, 1H), 2.81 (dd, J=8.1, 13.4 Hz, 1H), 2.36 (d, J=1.0 Hz, 3H), NH and NH ₂ not observed.	Rt = 1.81 min, m/z 406.2 [M+H] ⁺ (Method 1)
72	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methylbenzyl)benzyl)piperazin-1-yl)propan-1-one	1E-b / 1-(4-methylbenzyl)-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 7.99-7.97 (m, 1H), 7.31 (dd, J=1.7, 11.9 Hz, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.18-7.07 (m, 6H), 6.16 (dd, J=0.7, 5.4 Hz, 1H), 3.93 (t, J=6.9 Hz, 1H), 3.40-3.35 (m, 6H), 2.79 (dd, J=6.5, 13.1 Hz, 1H), 2.67 (dd, J=7.2, 13.2 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.34-2.29 (m, 2H), 2.27 (s, 3H), 2.19-2.07 (m, 1H), 2.02-1.95 (m, 1H), 1.75 (s, 2H).	Rt = 2.22 min, m/z 502.3 [M+H] ⁺ (Method 1)
73	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(3-methylbenzyl)benzyl)piperazin-1-yl)propan-1-one	1E-b / 1-(3-methylbenzyl)-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.39 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.33-7.04 (m, 8H), 6.16 (d, J=5.4 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.56-3.34 (m, 6H), 2.79 (dd, J=6.5, 13.1 Hz, 1H), 2.68 (dd, J=7.2, 13.1 Hz, 1H), 2.39 (s, 3H), 2.37-2.30 (m, 2H), 2.29 (s, 3H), 2.20-2.12 (m, 1H), 1.98 (t, J=7.5 Hz, 1H), 1.73 (s, 2H).	Rt = 2.25 min, m/z 502.3 [M+H] ⁺ (Method 1)

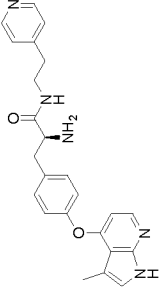
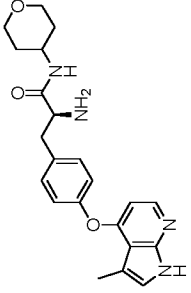
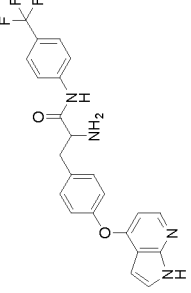
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
74	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-fluorobenzyl)piperazin-1-yl)propan-1-one	1E-b / 1-(4-fluorobenzyl)piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.34-7.22 (m, 4H), 7.17-7.11 (m, 4H), 6.16 (d, J=4.8 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.55-3.37 (m, 6H), 2.79 (dd, J=6.4, 13.1 Hz, 1H), 2.67 (dd, J=7.3, 13.1 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.37-2.28 (m, 2H), 2.19-2.13 (m, 1H), 2.06-1.76 (m, 3H).	Rt = 2.18 min, m/z 506.3 [M+H] ⁺ (Method 1)
75	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methoxybenzyl)piperazin-1-yl)propan-1-one	1E-b / 1-(4-methoxybenzyl)piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.38 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.33-7.08 (m, 6H), 6.87 (d, J=8.7 Hz, 2H), 6.16 (d, J=5.4 Hz, 1H), 3.93 (t, J=7.0 Hz, 1H), 3.73 (s, 3H), 3.54-3.34 (m, 6H), 2.79 (dd, J=6.5, 13.1 Hz, 1H), 2.67 (dd, J=7.3, 13.2 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.36-2.30 (m, 2H), 2.16-2.11 (m, 1H), 2.02-1.92 (m, 1H), 1.71 (s, 2H).	Rt = 2.12 min, m/z 518.3 [M+H] ⁺ (Method 1)
76	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenethylpropanamide	1E-b / 2-phenylethan-1-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.38 (s, 1H), 7.94 (d, J=5.5 Hz, 2H), 7.30-7.06 (m, 9H), 6.17-6.15 (m, 1H), 3.39 (dd, J=5.4, 7.8 Hz, 1H), 3.31-3.24 (m, 2H), 2.91 (dd, J=5.3, 13.4 Hz, 1H), 2.71-2.64 (m, 3H), 2.38 (d, J=1.0 Hz, 3H), 1.76 (s, 2H).	Rt = 2.73 min, m/z 433.3 [M+H] ⁺ (Method 1)

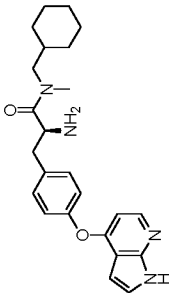
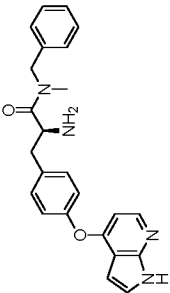
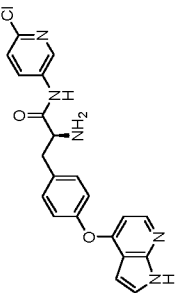
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
77	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperidin-1-yl)propan-1-one	1E-b / piperidine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.32 (dd, J=1.8, 11.9 Hz, 1H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.14-7.09 (m, 2H), 6.14 (dd, J=0.8, 5.4 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.55-3.45 (m, 1H), 3.42-3.35 (m, 3H), 2.80 (dd, J=6.3, 13.2 Hz, 1H), 2.66 (dd, J=7.3, 13.2 Hz, 1H), 2.38 (d, J=0.9 Hz, 3H), 1.74 (s, 2H), 1.58-1.42 (m, 4H), 1.37-1.28 (m, 1H), 1.25-1.15 (m, 1H).	Rt = 2.48 min, m/z 397.3 [M+H] ⁺ (Method 1)
78	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(isoquinolin-5-yl)propanamide	1E-b / isoquinolin-5-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 9.33 (s, 1H), 8.51 (d, J=6.0 Hz, 1H), 8.06 (d, J=7.6 Hz, 1H), 7.95 (d, J=8.2 Hz, 1H), 7.87 (d, J=5.5 Hz, 1H), 7.68 (t, J=7.9 Hz, 2H), 7.39 (dd, J=1.6, 11.9 Hz, 1H), 7.29-7.13 (m, 3H), 6.06 (d, J=4.8 Hz, 1H), 3.85 (t, J=6.5 Hz, 1H), 3.11 (dd, J=5.5, 13.6 Hz, 1H), 2.93 (dd, J=7.7, 13.4 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), NH and NH ₂ not observed.	Rt = 2.09 min, m/z 456.2 [M+H] ⁺ (Method 1)
79	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-morpholinopropyl)propanamide	1E-b / 3-morpholinopropan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.89 (t, J=5.7 Hz, 1H), 7.29-7.20 (m, 2H), 7.14-7.07 (m, 2H), 6.16 (d, J=4.8 Hz, 1H), 3.56-3.51 (m, 4H), 3.39 (dd, J=5.7, 7.4 Hz, 1H), 3.11-3.03 (m, 2H), 2.91 (dd, J=5.6, 13.3 Hz, 1H), 2.72 (dd, J=7.3, 13.2 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.32-2.25 (m, 4H), 2.21 (t, J=7.0 Hz, 2H), 1.84 (s, 2H), 1.54-1.45 (m, 2H).	Rt = 1.73 min, m/z 456.3 [M+H] ⁺ (Method 1)

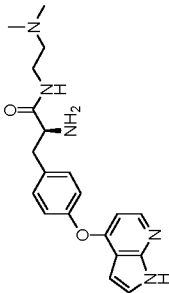
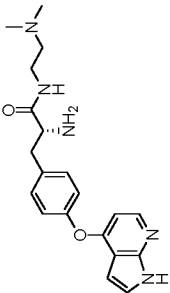
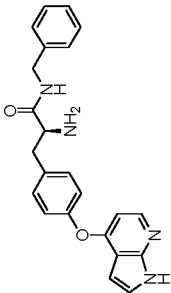
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
80	 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)propan-1-one	1E-b / 1-(pyridin-2-yl)piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.37 (s, 1H), 8.12 (dd, J=1.3, 4.9 Hz, 1H), 7.80 (d, J=5.4 Hz, 1H), 7.58-7.52 (m, 1H), 7.34 (dd, J=1.9, 11.9 Hz, 1H), 7.23 (t, J=8.4 Hz, 1H), 7.15-7.10 (m, 2H), 6.83 (d, J=8.6 Hz, 1H), 6.67 (dd, J=5.0, 6.6 Hz, 1H), 6.08 (d, J=4.9 Hz, 1H), 4.01 (t, J=6.9 Hz, 1H), 3.65-3.46 (m, 6H), 3.31-3.24 (m, 1H), 3.19-3.11 (m, 1H), 2.84 (dd, J=6.5, 13.1 Hz, 1H), 2.72 (dd, J=7.3, 13.2 Hz, 1H), 2.33 (d, J=1.0 Hz, 3H), 1.77 (s, 2H).	Rt = 2.04 min, m/z 475.3 [M+H] ⁺ (Method 1)
81	 2-amino-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-b / 5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.96 (m, 1H), 7.58 (s, 1H), 7.39-7.29 (m, 1H), 7.23-7.07 (m, 3H), 6.74 (m, 1H), 6.09 (m, 1H), 4.88-4.55 (m, 2H), 4.14-3.75 (m, 5H), 2.92-2.79 (m, 1H), 2.74-2.66 (m, 1H), 2.37 (d, J=1.0 Hz, 3H), 1.78 (br s, 2H).	Rt = 1.66 min, m/z 435.2 [M+H] ⁺ (Method 1)
82	 2-amino-N-((1-benzylpiperidin-4-yl)methyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-b / (1-benzylpiperidin-4-yl)methanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.81 (t, J=5.9 Hz, 1H), 7.32-7.18 (m, 6H), 7.14-7.06 (m, 2H), 6.14 (d, J=5.5 Hz, 1H), 3.42 (d, J=6.8 Hz, 1H), 3.39 (s, 2H), 3.01-2.82 (m, 3H), 2.76-2.68 (m, 3H), 2.37 (d, J=1 Hz, 3H), 1.86-1.76 (m, 4H), 1.49-1.44 (m, 2H), 1.33-1.23 (m, 1H), 1.11-0.99 (m, 2H).	Rt = 2.10 min, m/z 516.4 [M+H] ⁺ (Method 1)

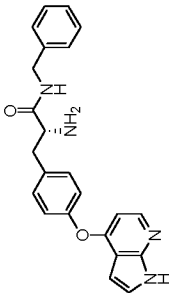
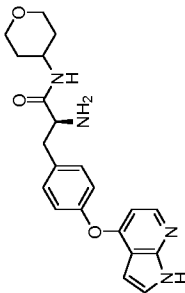
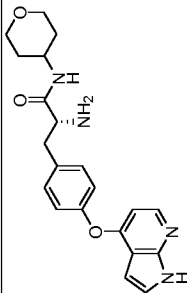
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
83	 2-amino-N-(1-benzylpiperidin-4-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-b / 1-benzylpiperidin-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.94 (d, J=5.4 Hz, 1H), 7.66 (d, J=7.9 Hz, 1H), 7.32-7.19 (m, 6H), 7.13-7.05 (m, 2H), 6.14 (d, J=5.0 Hz, 1H), 3.58-3.47 (m, 1H), 3.43 (s, 2H), 3.38 (t, J=6.8 Hz, 2H), 2.86 (dd, J=6.1, 13.2 Hz, 1H), 2.75-2.63 (m, 3H), 2.37 (d, J=0.9 Hz, 3H), 2.04-1.95 (m, 2H), 1.77 (s, 2H), 1.67-1.55 (m, 2H), 1.45-1.25 (m, 2H).	Rt = 2.08 min, m/z 502.3 [M+H] ⁺ (Method 1)
84	 First eluting rac-diastereoisomer (Diastereoisomer A) 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one	1E-b / rac-2-phenylpyrrolidine	Diastereoisomer A ¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.41 (s, 1H), 8.00-7.96 (m, 1H), 7.39-7.03 (m, 7H), 6.95-6.92 (m, 1H), 6.17-6.15 (m, 1H), 5.10-4.69 (m, 1H), 4.02-3.83 (m, 1H), 3.82-3.53 (m, 2H), 3.50 – 3.24 (m, 1H), 3.04-2.78 (m, 1H), 2.72-2.61 (m, 1H), 2.42-2.38 (m, 3H), 2.25-2.01 (m, 2H), 1.91-1.67 (m, 4H).	Rt = 2.87 min, m/z 459.3 [M+H] ⁺ (Method 1)
85	 Second eluting rac-diastereoisomer (Diastereoisomer B) 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one	1E-b / rac-2-phenylpyrrolidine	Diastereoisomer B ¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 8.00-7.96 (m, 1H), 7.38-6.99 (m, 7H), 6.52-6.46 (m, 1H), 6.15-6.08 (m, 1H), 5.29-4.99 (m, 1H), 3.89-3.75 (m, 1H), 3.67-3.52 (m, 1H), 3.30-3.23 (m, 1H), 2.86 (dd, J=6.7, 13.4 Hz, 1H), 2.70 (dd, J=7.6, 13.2 Hz, 1H), 2.40-2.36 (m, 5H), 2.12-2.02 (m, 1H), 1.84-1.67 (m, 4H).	Rt = 2.93 min, m/z 459.3 [M+H] ⁺ (Method 1)

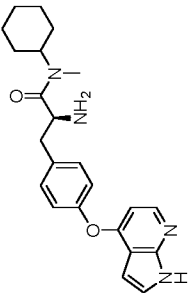
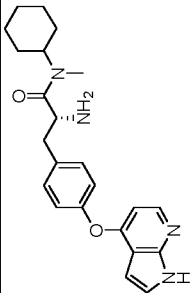
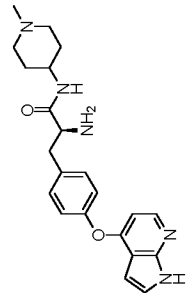
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
86	 (ee% = 79%) (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-c / 1-benzylpiperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.59 (s, 1H), 7.95 (d, J=5.4 Hz, 1H), 7.34-7.19 (m, 6H), 7.08 (dd, J=1.4, 8.3 Hz, 1H), 6.33 (d, J=5.4 Hz, 1H), 5.91 (s, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.48-3.42 (m, 4H), 3.39-3.25 (m, 4H), 2.80 (dd, J=6.4, 13.2 Hz, 1H), 2.67 (dd, J=7.4, 13.1 Hz, 1H), 2.35 (s, 3H), 2.33-2.28 (m, 1H), 2.25-2.19 (m, 1H), 2.14-2.04 (m, 1H), 1.71 (s, 2H).	Rt = 2.09 min, m/z 488.1 [M+H] ⁺ (Method 1)
87	 (S)-2-amino-N-(3-methoxypropyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	1E-d / 3-methoxypropan-1-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.36 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.82 (t, J=5.7 Hz, 1H), 7.26 (d, J=8.5 Hz, 2H), 7.14-7.09 (m, 1H), 7.05 (d, J=8.6 Hz, 2H), 6.24 (d, J=5.4 Hz, 1H), 3.40-3.35 (m, 1H), 3.25 (t, J=6.3 Hz, 2H), 3.20 (s, 3H), 3.16-3.01 (m, 2H), 2.89 (dd, J=5.6, 13.3 Hz, 1H), 2.67 (dd, J=7.6, 13.3 Hz, 1H), 2.33-2.33 (m, 3H), 1.72-1.72 (m, 2H), 1.62-1.52 (m, 2H).	Rt = 2.08 min, m/z 383.2 [M+H] ⁺ (Method 1)
88	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1E-d / 1-benzylpiperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.36 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.34-7.24 (m, 7H), 7.14-7.10 (m, 1H), 7.06 (d, J=8.6 Hz, 2H), 6.24 (d, J=5.4 Hz, 1H), 3.91 (t, J=6.9 Hz, 1H), 3.53-3.45 (m, 1H), 3.41 (s, 2H), 3.40-3.35 (m, 2H), 3.27 (d, J=3.1 Hz, 1H), 2.77 (dd, J=7.0, 13.0 Hz, 1H), 2.67 (dd, J=6.9, 13.0 Hz, 1H), 2.34 (d, J=1.0 Hz, 3H), 2.33-2.26 (m, 2H), 2.18-2.14 (m, 1H), 1.98-1.92 (m, 1H), 1.70 (s, 2H).	Rt = 1.94 min, m/z 470.3 [M+H] ⁺ (Method 1)

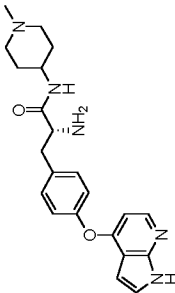
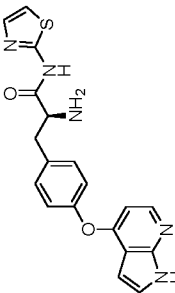
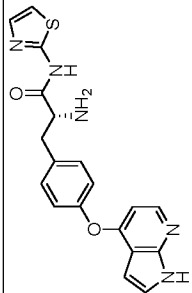
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
89	 (S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide	1E-d / 2-(pyridin-4-yl)ethan-1-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.36 (s, 1H), 8.45 (dd, J=1.6, 4.4 Hz, 2H), 7.99-7.94 (m, 2H), 7.27-7.18 (m, 4H), 7.14-7.09 (m, 1H), 7.06 (d, J=18.2 Hz, 2H), 6.24 (d, J=5.4 Hz, 1H), 3.41 – 3.30 (m, 2H), 2.88 (dd, J=5.3, 13.3 Hz, 1H), 2.71 (t, J=6.9 Hz, 2H), 2.64 (dd, J=7.2, 13.5 Hz, 1H), 2.33 (s, 3H), 1.76-1.71 (m, 2H).	Rt = 1.67 min, m/z 416.3 [M+H] ⁺ (Method 1)
90	 (S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide	1E-d / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.35 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.26 (d, J=8.6 Hz, 2H), 7.13-7.09 (m, 1H), 7.06-7.03 (m, 2H), 6.24 (d, J=5.4 Hz, 1H), 3.83-3.69 (m, 3H), 3.42-3.38 (m, 3H), 2.86 (dd, J=6.2, 13.2 Hz, 1H), 2.69 (dd, J=7.5, 13.3 Hz, 1H), 2.32 (d, J=1.0 Hz, 3H), 1.66-1.54 (m, 2H), 1.43-1.22 (m, 2H).	Rt = 2.06 min, m/z 395.0 [M+H] ⁺ (Method 1)
91	 Complete racemisation occurred during synthesis 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide	1E-f / 4-(trifluoromethyl)aniline	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.69 (s, 1H), 8.02 (d, J=5.4 Hz, 1H), 7.83 (d, J=8.4 Hz, 2H), 7.67 (d, J=8.6 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 7.28 (dd, J=2.6, 3.3 Hz, 1H), 7.08 (d, J=8.5 Hz, 2H), 6.32 (d, J=5.4 Hz, 1H), 6.14 (dd, J=2.0, 3.5 Hz, 1H), 3.63 (t, J=6.7 Hz, 1H), 3.00 (dd, J=5.9, 13.4 Hz, 1H), 2.82 (dd, J=7.7, 13.4 Hz, 1H).	Rt = 2.78 min, m/z 441.2 [M+H] ⁺ (Method 1)

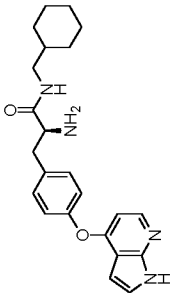
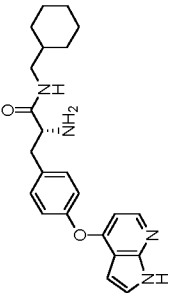
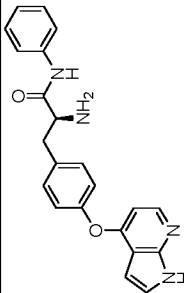
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
92	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide	1E-e / cyclohexyl-N-methylmethanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.72 (s, 1H), 8.08-8.05 (m, 1H), 7.36-7.32 (m, 1H), 7.27 (dd, J=8.6, 16.0 Hz, 2H), 7.10-7.04 (m, 2H), 6.38-6.35 (m, 1H), 6.19-6.16 (m, 1H), 3.89-3.77 (2 x t, 1H), 3.23 (dd, J=7.2, 13.0 Hz, 1H), 2.99-2.92 (m, 1H), 2.88 and 2.77 (2 x s, 3H), 2.86-2.78 (m, 1H), 2.71-2.61 (m, 1H), 1.74 (s, 2H), 1.62-1.42 (m, 6H), 1.19-1.02 (m, 3H), 0.96-0.75 (m, 2H).	Rt = 2.80 min, m/z 407.3 [M+H] ⁺ (Method 1)
93	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-N-methylpropanamide	1E-e / N-methyl-1-phenylmethanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.72 (s, 1H), 8.08-8.05 (m, 1H), 7.35-7.19 (m, 6H), 7.14-7.03 (m, 4H), 6.40-6.34 (m, 1H), 6.20-6.17 (m, 1H), 4.61-4.29 (m, 2H), 4.03-3.82 (2 x t, 1H), 2.87 (dd, J=7.0, 13.1 Hz, 1H), 2.82-2.77 (2 x s, 3H), 2.76-2.65 (m, 1H), 2.35 (s, 2H).	Rt = 2.49 min, m/z 401.2 [M+H] ⁺ (Method 1)
94	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(6-chloropyridin-3-yl)propanamide	1E-e / 6-chloropyridin-3-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.70 (s, 1H), 8.62 (d, J=2.7 Hz, 1H), 8.12 (dd, J=2.8, 8.7 Hz, 1H), 8.03 (d, J=5.4 Hz, 1H), 7.47 (d, J=8.7 Hz, 1H), 7.31 (d, J=8.5 Hz, 2H), 7.29 (dd, J=2.6, 3.4 Hz, 1H), 7.08 (d, J=8.6 Hz, 2H), 6.32 (d, J=5.4 Hz, 1H), 6.14 (dd, J=2.0, 3.4 Hz, 1H), 3.62 (t, J=6.9 Hz, 1H), 2.99 (dd, J=5.9, 13.3 Hz, 1H), 2.82 (dd, J=7.6, 13.3 Hz, 1H).	Rt = 2.70 min, m/z 408.2 [M+H] ⁺ (Method 3)

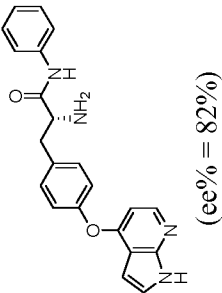
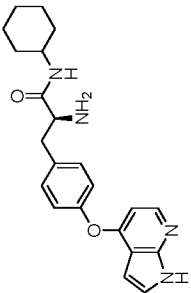
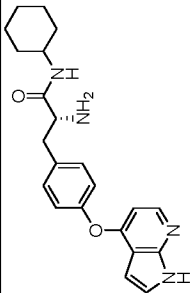
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
95	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide	1E-e / N,N'-dimethylethane-1,2-diamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.72 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.79 (t, J=5.6 Hz, 1H), 7.34 (dd, J=2.4, 3.4 Hz, 1H), 7.28 (d, J=8.5 Hz, 2H), 7.09 (d, J=8.5 Hz, 2H), 6.39 (d, J=5.4 Hz, 1H), 6.20 (dd, J=1.9, 3.4 Hz, 1H), 3.38 (dd, J=5.2, 7.9 Hz, 1H), 3.17-3.10 (m, 2H), 2.93 (dd, J=5.2, 13.3 Hz, 1H), 2.67 (dd, J=7.9, 13.3 Hz, 1H), 2.23 (t, J=6.7 Hz, 2H), 2.12 (s, 6H), 1.76 (s, 2H).	Rt = 2.89 min, m/z 368.2 [M+H] ⁺ (Method 1)
96	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide	1E-g / N,N'-dimethylethane-1,2-diamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.71 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.79 (t, J=5.6 Hz, 1H), 7.34 (dd, J=2.5, 3.3 Hz, 1H), 7.28 (d, J=8.5 Hz, 2H), 7.09 (d, J=8.5 Hz, 2H), 6.39 (d, J=5.3 Hz, 1H), 6.20 (dd, J=1.9, 3.5 Hz, 1H), 3.38 (dd, J=5.2, 7.9 Hz, 1H), 3.17-3.09 (m, 2H), 2.93 (dd, J=5.2, 13.4 Hz, 1H), 2.66 (dd, J=8.0, 13.3 Hz, 1H), 2.23 (t, J=6.7 Hz, 2H), 2.12 (s, 6H), 1.75 (s, 2H).	Rt = 2.91 min, m/z 368.2 [M+H] ⁺ (Method 1)
97	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide	1E-e / benzylamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.71 (s, 1H), 8.33 (t, J=6.0 Hz, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.34 (dd, J=2.5, 3.4 Hz, 1H), 7.31-7.15 (m, 7H), 7.07 (d, J=8.6 Hz, 2H), 6.39 (d, J=5.4 Hz, 1H), 6.21 (dd, J=1.9, 3.5 Hz, 1H), 4.34-4.20 (m, 2H), 3.47 (dd, J=5.8, 7.5 Hz, 1H), 2.95 (dd, J=5.7, 13.3 Hz, 1H), 2.72 (dd, J=7.8, 13.4 Hz, 1H), 1.77 (s, 2H).	Rt = 2.32 min, m/z 387.2 [M+H] ⁺ (Method 1)

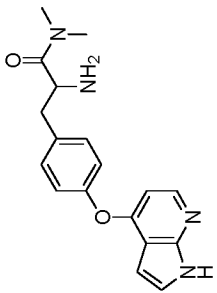
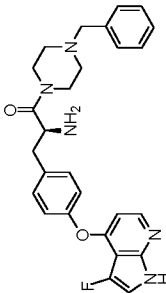
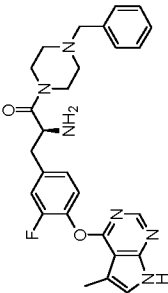
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
98	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide	1E-g / benzylamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.32 (t, J=6.0 Hz, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.34 (dd, J=2.5, 3.4 Hz, 1H), 7.31-7.15 (m, 7H), 7.07 (d, J=8.6 Hz, 2H), 6.39 (d, J=5.4 Hz, 1H), 6.21 (dd, J=1.9, 3.4 Hz, 1H), 4.33-4.20 (m, 2H), 3.47 (dd, J=5.8, 7.5 Hz, 1H), 2.95 (dd, J=5.6, 13.3 Hz, 1H), 2.72 (dd, J=7.7, 13.3 Hz, 1H), 1.77 (s, 2H).	Rt = 2.33 min, m/z 387.2 [M+H] ⁺ (Method 1)
99	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide	1E-e / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.71 (d, J=7.8 Hz, 1H), 7.34 (dd, J=2.4, 3.3 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.38 (d, J=5.4 Hz, 1H), 6.22-6.18 (m, 1H), 3.83-3.71 (m, 3H), 3.39-3.28 (m, 3H), 2.87 (dd, J=6.0, 13.2 Hz, 1H), 2.70 (dd, J=7.4, 13.2 Hz, 1H), 1.71 (s, 2H), 1.68-1.56 (m, 2H), 1.43-1.26 (m, 2H).	Rt = 1.85 min, m/z 381.2 [M+H] ⁺ (Method 1)
100	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide	1E-g / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.34 (dd, J=2.5, 3.3 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 7.08 (d, J=8.6 Hz, 2H), 6.38 (d, J=5.4 Hz, 1H), 6.21-6.19 (m, 1H), 3.83-3.72 (m, 3H), 3.40-3.27 (m, 3H), 2.87 (dd, J=6.0, 13.2 Hz, 1H), 2.70 (dd, J=7.1, 13.0 Hz, 1H), 1.74 (s, 2H), 1.66-1.56 (m, 2H), 1.43-1.26 (m, 2H).	Rt = 1.86 min, m/z 381.2 [M+H] ⁺ (Method 1)

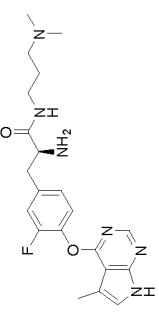
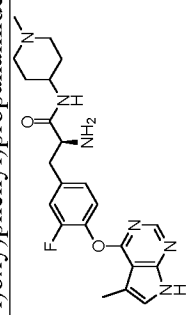
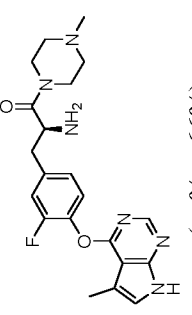
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
101	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide	1E-e / N-methylcyclohexan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.72 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.37-7.32 (m, 1H), 7.30-7.23 (m, 2H), 7.10-7.05 (m, 2H), 6.37-6.34 (m, 1H), 6.22-6.18 (m, 1H), 4.30-4.16 and 3.56-3.45 (m, 1H), 3.92-3.82 (m, 1H), 2.83-2.73 (m, 1H), 2.66-2.73 (m, 1H), 2.64 and 2.65 (s, 3H), 1.72 (s, 2H), 1.66-1.56 (m, 4H), 1.49-1.00 (m, 6H).	Rt = 2.50 min, m/z 393.3 [M+H] ⁺ (Method 1)
102	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide	1E-g / N-methylcyclohexan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.72 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.36-7.32 (m, 1H), 7.27-7.30 (m, 2H), 7.10-7.05 (m, 2H), 6.38-6.33 (m, 1H), 6.22-6.18 (m, 1H), 4.29-4.17 and 3.56-3.45 (m, 1H), 3.92-3.82 (m, 1H), 2.83-2.73 (m, 1H), 2.65-2.72 (m, 1H), 2.64 – 2.66 (s, 3H), 1.72 (s, 2H), 1.66-1.56 (m, 4H), 1.49-1.00 (m, 6H).	Rt = 2.51 min, m/z 393.3 [M+H] ⁺ (Method 1)
103	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide	1E-e / 1-methylpiperidin-4-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.05 (d, J=5.4 Hz, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.34 (dd, J=2.4, 3.3 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 7.08 (d, J=8.6 Hz, 2H), 6.37 (d, J=5.4 Hz, 1H), 6.20 (dd, J=1.8, 3.4 Hz, 1H), 3.52-3.41 (m, 1H), 3.37 (t, J=6.6 Hz, 1H), 2.86 (dd, J=5.9, 13.3 Hz, 1H), 2.72-2.58 (m, 3H), 2.12 (s, 3H), 1.95-1.85 (m, 2H), 1.69 (s, 2H), 1.65-1.57 (m, 2H), 1.42-1.25 (m, 2H).	Rt = 2.91 min, m/z 394.2 [M+H] ⁺ (Method 1)

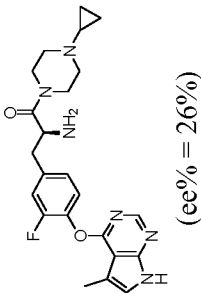
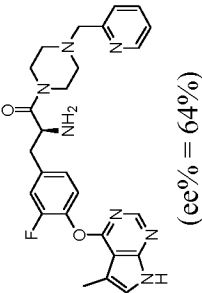
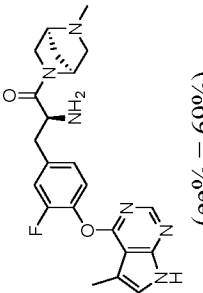
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
104	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide	1E-g / 1-methylpiperidin-4-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.73-11.68 (m, 1H), 8.05 (d, J=5.4 Hz, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.34 (dd, J=2.5, 3.4 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.37 (d, J=5.4 Hz, 1H), 6.20 (dd, J=1.9, 3.5 Hz, 1H), 3.52-3.42 (m, 1H), 3.37 (t, J=6.7 Hz, 1H), 2.86 (dd, J=6.0, 13.2 Hz, 1H), 2.72-2.59 (m, 3H), 2.12 (s, 3H), 1.95-1.86 (m, 2H), 1.71 (s, 2H), 1.67-1.55 (m, 2H), 1.42-1.25 (m, 2H).	Rt = 2.91 min, m/z 394.2 [M+H] ⁺ (Method 1)
105	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide	1E-e / 2-aminothiazole	¹ H NMR (400 MHz, d6-DMSO) δ 11.69 (s, 1H), 8.04 (d, J=5.4 Hz, 1H), 7.48 (d, J=3.5 Hz, 1H), 7.32-7.28 (m, 3H), 7.21 (d, J=3.5 Hz, 1H), 7.07 (d, J=8.6 Hz, 2H), 6.33 (d, J=5.4 Hz, 1H), 6.14 (dd, J=1.8, 3.4 Hz, 1H), 5.27-5.27 (m, 3H), 3.74 (dd, J=6.1, 7.9 Hz, 1H), 2.99 (dd, J=5.9, 13.4 Hz, 1H), 2.79 (dd, J=8.0, 13.4 Hz, 1H).	Rt = 2.00 min, m/z 380.0 [M+H] ⁺ (Method 1)
106	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide (ee% = 83%)	1E-g / 2-aminothiazole	¹ H NMR (400 MHz, d6-DMSO) δ 11.69 (s, 1H), 8.04 (d, J=5.4 Hz, 1H), 7.48 (d, J=3.5 Hz, 1H), 7.30 (d, J=8.2 Hz, 3H), 7.21 (d, J=3.5 Hz, 1H), 7.07 (d, J=8.4 Hz, 2H), 6.33 (d, J=5.4 Hz, 1H), 6.14 (d, J=1.7 Hz, 1H), 5.27-5.27 (m, 3H), 3.74 (m, 1H), 2.99 (dd, J=5.8, 13.4 Hz, 1H), 2.79 (dd, J=8.0, 13.2 Hz, 1H).	Rt = 2.00 min, m/z 380.1 [M+H] ⁺ (Method 1)

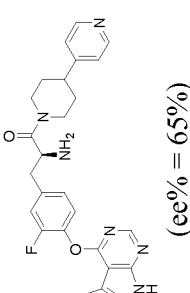
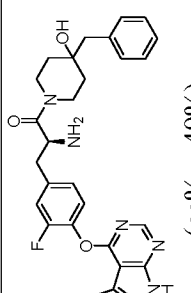
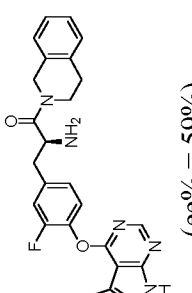
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
107	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide	1E-e / cyclohexylmethanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.76 (t, J=5.9 Hz, 1H), 7.34 (dd, J=2.6, 3.3 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.38 (d, J=5.4 Hz, 1H), 6.20 (dd, J=2.0, 3.5 Hz, 1H), 3.39 (dd, J=5.9, 7.5 Hz, 1H), 2.96-2.80 (m, 3H), 2.68 (dd, J=7.4, 13.2 Hz, 1H), 1.78 (s, 2H), 1.67-1.53 (m, 5H), 1.38-1.28 (m, 1H), 1.21-1.05 (m, 3H), 0.84-0.74 (m, 2H).	Rt = 2.59 min, m/z 393.2 [M+H] ⁺ (Method 1)
108	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide (ee% = 83%)	1E-g / cyclohexylmethanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.71 (s, 1H), 8.06 (d, J=5.4 Hz, 1H), 7.76 (t, J=5.9 Hz, 1H), 7.34 (dd, J=2.5, 3.4 Hz, 1H), 7.27 (d, J=8.6 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.38 (d, J=5.4 Hz, 1H), 6.20 (dd, J=1.9, 3.5 Hz, 1H), 3.39 (dd, J=6.0, 7.3 Hz, 1H), 2.96-2.80 (m, 3H), 2.72-2.65 (m, 1H), 1.72 (s, 2H), 1.67-1.55 (m, 5H), 1.37-1.28 (m, 1H), 1.16-1.08 (m, 3H), 0.80 (q, J=11.4 Hz, 2H).	Rt = 2.55 min, m/z 393.2 [M+H] ⁺ (Method 3)
109	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide (ee% = 85%)	1E-e / aniline	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.69 (s, 1H), 9.81 (s, 1H), 8.03 (d, J=5.4 Hz, 1H), 7.60 (dd, J=1.1, 8.6 Hz, 2H), 7.34-7.26 (m, 5H), 7.11-7.02 (m, 3H), 6.33 (d, J=5.4 Hz, 1H), 6.15 (dd, J=2.0, 3.5 Hz, 1H), 3.59 (dd, J=5.8, 7.7 Hz, 1H), 3.00 (dd, J=5.7, 13.4 Hz, 1H), 2.79 (dd, J=7.9, 13.4 Hz, 1H), 1.98-1.98 (m, 2H).	Rt = 2.25 min, m/z 373.2 [M+H] ⁺ (Method 1)

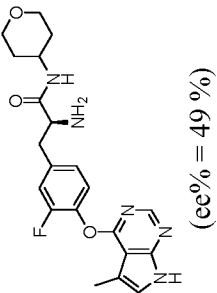
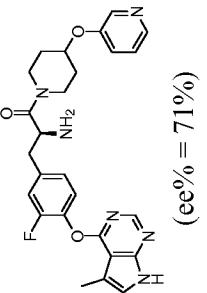
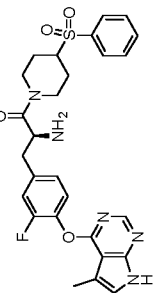
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
110	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide (ee% = 82%)	1E-g / aniline	¹ H NMR (400 MHz, d6-DMSO) δ 11.69 (s, 1H), 9.82 (s, 1H), 8.03 (d, J=5.4 Hz, 1H), 7.61-7.59 (m, 2H), 7.34-7.26 (m, 5H), 7.11-7.01 (m, 3H), 6.33 (d, J=5.4 Hz, 1H), 6.15 (dd, J=1.9, 3.5 Hz, 1H), 3.59 (dd, J=6.0, 7.5 Hz, 1H), 3.00 (dd, J=5.7, 13.3 Hz, 1H), 2.79 (dd, J=7.8, 13.3 Hz, 1H), 1.94 (s, 2H).	Rt = 2.22 min, m/z 373.2 [M+H] ⁺ (Method 3)
111	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide	1E-e / cyclohexanamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.71 (s, 1H), 8.05 (d, J=5.4 Hz, 1H), 7.58 (d, J=8.1 Hz, 1H), 7.34 (dd, J=2.5, 3.4 Hz, 1H), 7.27 (d, J=8.6 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.37 (d, J=5.4 Hz, 1H), 6.21 (dd, J=2.0, 3.5 Hz, 1H), 3.55-3.46 (m, 1H), 3.36 (dd, J=6.1, 7.3 Hz, 1H), 2.86 (dd, J=5.9, 13.3 Hz, 1H), 2.69 (dd, J=7.4, 13.4 Hz, 1H), 1.76 (s, 2H), 1.72-1.61 (m, 4H), 1.29-1.02 (m, 6H).	Rt = 2.38 min, m/z 379.2 [M+H] ⁺ (Method 1)
112	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide (ee% = 84%)	1E-g / cyclohexanamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.71 (s, 1H), 8.05 (d, J=5.4 Hz, 1H), 7.57 (d, J=8.1 Hz, 1H), 7.34 (dd, J=2.5, 3.3 Hz, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H), 6.37 (d, J=5.4 Hz, 1H), 6.21 (dd, J=1.9, 3.5 Hz, 1H), 3.56-3.46 (m, 1H), 3.40-3.34 (m, 1H), 2.86 (dd, J=5.9, 13.2 Hz, 1H), 2.71-2.65 (m, 1H), 1.75-1.58 (m, 6H), 1.57-1.49 (m, 1H), 1.29-1.02 (m, 5H).	Rt = 2.34 min, m/z 379.2 [M+H] ⁺ (Method 3)

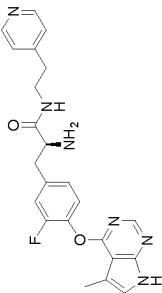
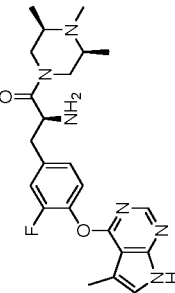
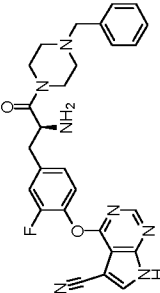
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
113	 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N,N-dimethylpropanamide	1E-f / dimethyl-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.72 (s, 1H), 8.08 (d, J=5.4 Hz, 1H), 7.35 (dd, J=2.4, 3.3 Hz, 1H), 7.28 (d, J=8.7 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 6.39 (d, J=5.4 Hz, 1H), 6.17 (dd, J=1.7, 3.4 Hz, 1H), 4.01 (t, J=6.9 Hz, 1H), 3.83-3.65 (s, 2H), 2.86-2.79 (m, 1H), 2.84 (s, 3H), 2.80 (s, 3H), 2.76-2.69 (m, 1H).	Rt = 1.77 min, m/z 325.1 [M+H] ⁺ (Method 3)
114	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	1E-h / 1-benzyl-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.54 (s, 1H), 8.06 (d, J=5.5 Hz, 1H), 7.36-7.24 (m, 8H), 7.12 (d, J=8.6 Hz, 2H), 6.29 (d, J=5.4 Hz, 1H), 3.91 (dd, J=6.9, 6.9 Hz, 1H), 3.45-3.37 (m, 5H), 3.34-3.21 (m, 2H), 2.81-2.64 (m, 2H), 2.34-2.29 (m, 2H), 2.22-2.18 (m, 1H), 2.00 (d, J=7.7 Hz, 1H), 1.24 (s, 1H).	Rt = 2.16 min, m/z 474.0 [M+H] ⁺ (Method 1)
115	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one (ee% = 87%)	1E-i / 1-benzylpiperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.90 (s, 1H), 8.19 (s, 1H), 7.33-7.21 (m, 8H), 7.09 (dd, J=1.4, 8.3 Hz, 1H), 3.93 (t, J=6.9 Hz, 1H), 3.53-3.37 (m, 6H), 2.79 (dd, J=6.4, 13.2 Hz, 1H), 2.68 (dd, J=7.3, 13.1 Hz, 1H), 2.43 (d, J=1.1 Hz, 3H), 2.36-2.27 (m, 2H), 2.27-2.19 (m, 1H), 2.09-2.03 (m, 1H), 1.70 (s, 2H).	Rt = 2.45 min, m/z 489.3 [M+H] ⁺ (Method 1)

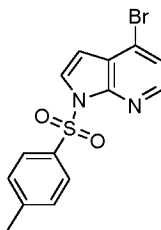
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
116	 (S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propanamide	1E-i / N,N-dimethylpropane-1,3-diamine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.20 (s, 1H), 7.88 (t, J=5.7 Hz, 1H), 7.33-7.19 (m, 3H), 7.10-7.06 (m, 1H), 3.43-3.36 (m, 2H), 3.13-2.99 (m, 3H), 2.92 (dd, J=5.5, 13.4 Hz, 1H), 2.69 (dd, J=7.9, 13.4 Hz, 1H), 2.41 (d, J=1.0 Hz, 3H), 2.16-2.09 (m, 2H), 2.08 (s, 6H), 1.52-1.43 (m, 2H).	Rt = 2.02 min, m/z 415.1 [M+H] ⁺ (Method 1)
117	 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide (ee% = 81%)	1E-i / 1-methylpiperidin-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.19 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.30 (t, J=8.2 Hz, 1H), 7.26-7.18 (m, 2H), 7.10-7.06 (m, 1H), 3.54-3.44 (m, 1H), 3.39 (dd, J=5.7, 7.7 Hz, 1H), 2.89 (dd, J=5.5, 13.4 Hz, 1H), 2.72-2.58 (m, 3H), 2.42 (d, J=1.0 Hz, 3H), 2.13 (s, 3H), 1.97-1.86 (m, 2H), 1.70-1.60 (m, 2H), 1.45-1.31 (m, 2H).	Rt = 2.01 min, m/z 427.1 [M+H] ⁺ (Method 1)
118	 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]piperazin-4-yl)oxy)phenyl)-N-(1-methylpiperazin-1-yl)propan-1-one (ee% = 66%)	1E-i / 1-methylpiperazine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.20 (s, 1H), 7.31 (t, J=8.2 Hz, 1H), 7.27-7.19 (m, 2H), 7.11-7.06 (m, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.45-3.16 (m, 6H), 2.80 (dd, J=6.5, 13.2 Hz, 1H), 2.68 (dd, J=7.3, 13.1 Hz, 1H), 2.41 (s, 3H), 2.33-2.26 (m, 2H), 2.13 (s, 3H), 2.07-1.97 (m, 1H), 1.73 (s, 1H).	Rt = 1.97 min, m/z 413.1 [M+H] ⁺ (Method 1)

Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
119	 (ee% = 26%) (S)-2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one	1E-i / 1-cyclopropylpiperazine	¹ H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 8.18 (s, 1H), 7.31 (t, J=8.2 Hz, 1H), 7.27-7.20 (m, 2H), 7.09 (dd, J=1.4, 8.2 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.60-3.15 (m, 4H), 2.80 (dd, J=6.6, 13.1 Hz, 1H), 2.69 (dd, J=7.1, 13.1 Hz, 1H), 2.48-2.44 (m, 2H), 2.40 (d, J=1.0 Hz, 3H), 2.38-2.33 (m, 1H), 2.21 (dd, J=3.8, 7.1 Hz, 1H), 1.74 (s, 2H), 1.59-1.52 (m, 1H), 0.46-0.37 (m, 2H), 0.34-0.28 (m, 2H).	Rt = 2.19 min, m/z 439.1 [M+H] ⁺ (Method 1)
120	 (ee% = 64%) (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one	1E-i / 1-(pyridin-2-ylmethyl)piperazine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.49 (dd, J=0.9, 3.9 Hz, 1H), 8.20 (s, 1H), 7.76 (dt, J=1.8, 7.7 Hz, 1H), 7.43 (d, J=7.8 Hz, 1H), 7.33-7.22 (m, 4H), 7.09 (dd, J=1.4, 8.2 Hz, 1H), 3.97-3.91 (m, 1H), 3.57 (s, 2H), 3.48-3.42 (m, 4H), 2.80 (dd, J=6.5, 13.2 Hz, 1H), 2.67 (dd, J=7.4, 13.2 Hz, 1H), 2.42 (d, J=1.0 Hz, 3H), 2.41-2.24 (m, 3H), 2.19-2.15 (m, 1H), 1.72 (s, 2H).	Rt = 2.24 min, m/z 490.4 [M+H] ⁺ (Method 1)
121	 (ee% = 69%) 2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one	1E-i / (1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]heptane	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.19-8.17 (m, 1H), 7.33-7.22 (m, 3H), 7.14-7.08 (m, 1H), 4.51 & 4.27 (2xs, 1H), 3.84-3.47 (m, 3H), 3.18-3.08 (m, 1H), 3.02-2.95 (m, 1H), 2.83-2.67 (m, 4H), 2.43-2.39 (m, 3H), 2.31-2.27 (m, 2H), 2.17-2.02 (m, 2H), 1.76-1.67 (m, 1H), 1.52 & 1.36 (2xd, J=9.6 Hz, 1H).	Rt = 1.97 min, m/z 425.3 [M+H] ⁺ (Method 3)

Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
122	 (ee% = 65%) (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one	1E-i / 4-(piperidin-4-yl)pyridine	¹ H NMR (400 MHz, DMSO) δ 11.91 (s, 1H), 8.47 (d, J=5.7 Hz, 1H), 8.37 (d, J=5.7 Hz, 1H), 8.20 & 8.09 (2xs, 1H), 7.36-7.22 (m, 5H), 7.18-7.11 (m, 2H), 4.59-4.53 (m, 1H), 4.11-3.97 (m, 2H), 3.08 & 2.96 (2xt, J=12.7 Hz, 1H), 2.89-2.82 (m, 1H), 2.78-2.70 (m, 1H), 2.68 – 2.51 (m, 1H), 2.40 (2xs, 3H), 1.87-1.69 (m, 4H), 1.68-1.57 & 1.52-1.41 (m, 1H), 1.33-1.23 & 1.09-0.98 (m, 1H).	Rt = 2.24 min, m/z 475.3 [M+H] ⁺ (Method 3)
123	 (ee% = 49%) (S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one	1E-i / 4-benzylpiperidin-4-ol	¹ H NMR (400 MHz, CDCl ₃) δ 9.02 (s, 1H), 8.32 & 8.24 (s, 1H), 7.35-7.27 (m, 3H), 7.24-7.02 (m, 5H), 6.94 (d, J=10.3 Hz, 1H), 4.47-4.43 & 4.30-4.26 (m, 1H), 4.04-3.95 (m, 1H), 3.57-3.52 (m, 1H), 3.38-2.78 (m, 5H), 2.76 (s, 1H), 2.67 (s, 1H), 2.49 & 2.41 (2xs, 3H), 1.57-1.37 & 0.84-0.77 (m, 6H).	Rt = 3.06 min, m/z 504.2 [M+H] ⁺ (Method 1)
124	 (ee% = 59%) (S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one	1E-i / 1,2,3,4-tetrahydroisoquinoline	¹ H NMR (400 MHz, DMSO) δ 11.89 (s, 1H), 8.11 (d, J=16.1 Hz, 1H), 7.32-7.05 (m, 8H), 4.77-4.65 (m, 1H), 4.53 (d, J=16.8 Hz, 1H), 4.07-3.99 (m, 1H), 3.80-3.57 (m, 2H), 2.90-2.67 (m, 4H), 2.42 (d, J=2.1 Hz, 3H), 1.82-1.82 (m, 2H).	Rt = 3.18 min, m/z 446.3 [M+H] ⁺ (Method 3)

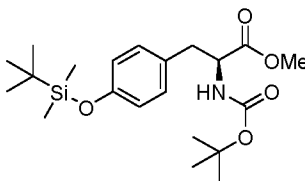
Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
125	 (ee% = 49 %) (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide	1E-i / tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.19 (s, 1H), 7.76 (d, J=7.9 Hz, 1H), 7.30 (t, J=8.3 Hz, 1H), 7.25-7.19 (m, 2H), 7.08 (dd, J=1.5, 8.3 Hz, 1H), 3.84-3.69 (m, 3H), 3.42-3.33 (m, 3H), 2.90 (dd, J=5.6, 13.2 Hz, 1H), 2.70 (dd, J=7.9, 13.2 Hz, 1H), 2.41 (d, J=0.9 Hz, 3H), 1.79 (s, 2H), 1.69-1.60 (m, 2H), 1.45-1.31 (m, 2H).	Rt = 2.64 min, m/z 414.3 [M+H] ⁺ (Method 3)
126	 (ee% = 71%) (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yloxy)piperidin-1-yl)propan-1-one	1E-i / 3-(piperidin-4-yloxy)pyridine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.29 (dd, J=2.8, 14.6 Hz, 1H), 8.20-8.15 (m, 2H), 7.46-7.41 (m, 1H), 7.34-7.22 (m, 4H), 7.11 (d, J=8.2 Hz, 1H), 4.69-4.65 (m, 1H), 3.98 (t, J=6.8 Hz, 1H), 3.91-3.87 (m, 1H), 3.84-3.65 (m, 1H), 3.43-3.19 (m, 3H), 2.84 (dd, J=6.1, 13.0 Hz, 1H), 2.71-2.64 (m, 1H), 2.42 (s, 3H), 1.99-1.71 (m, 2H), 1.70-1.28 (m, 3H).	Rt = 2.53 min, m/z 491.4 [M+H] ⁺ (Method 3)
127	 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one	1E-i / 4-(benzenesulfonyl)piperidine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.24-8.16 (m, 1H), 7.87-7.65 (m, 5H), 7.30-7.22 (m, 3H), 7.11-7.03 (m, 1H), 4.55-4.41 (m, 1H), 4.12-4.00 (m, 1H), 3.95-3.90 (m, 1H), 3.58-3.51 (m, 1H), 3.05-2.83 (m, 1H), 2.80 (dd, J=5.2, 13.3 Hz, 1H), 2.71-2.52 (m, 2H), 2.45-2.40 (m, 3H), 1.93-1.49 (m, 4H), 1.41-1.08 (m, 2H).	Rt = 3.02 min, m/z 538.1 [M+H] ⁺ (Method 1)

Ex	Structure / Name	Intermediate 1E / Amine	¹ H NMR	LC-MS
128	 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide	1E-i / 2-(pyridin-4-yl)ethan-1-amine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.45 (dd, J=1.6, 4.4 Hz, 2H), 8.17 (s, 1H), 7.99 (t, J=5.8 Hz, 1H), 7.30 (t, J=8.2 Hz, 1H), 7.25-7.18 (m, 4H), 7.07 (dd, J=1.4, 8.2 Hz, 1H), 3.42-3.36 (m, 3H), 2.90 (dd, J=5.1, 13.4 Hz, 1H), 2.72 (t, J=7.1 Hz, 2H), 2.64 (dd, J=8.1, 13.4 Hz, 1H), 2.42 (d, J=1.1 Hz, 3H), 1.77 (s, 2H).	Rt = 2.09 min, m/z 435.2 [M+H] ⁺ (Method 1)
129	 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one	1E-i / (2S,6R)-1,2,6-trimethylpiperazine	¹ H NMR (400 MHz, DMSO) δ 11.90 (s, 1H), 8.20 (d, J=3.9 Hz, 1H), 7.34-7.26 (m, 1H), 7.26-7.21 (m, 2H), 7.08 (d, J=8.1 Hz, 1H), 4.25-4.15 (m, 1H), 4.03-3.96 (m, 1H), 3.81-3.65 (m, 1H), 2.83-2.52 (m, 4H), 2.42-2.40 (m, 3H), 2.26 (dd, J=11.1, 12.7 Hz, 1H), 2.14 (s, 1H), 2.08-2.05 (m, 3H), 2.00-1.68 (m, 2H), 1.03-0.92 (m, 6H).	Rt = 2.06 min, m/z 441.3 [M+H] ⁺ (Method 1)
130	 (S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile	1E-j / 1-benzylpiperazine	¹ H NMR (400 MHz, d6-DMSO) δ 8.43 (s, 1H), 8.37 (s, 1H), 7.40-7.20 (m, 8H), 7.11 (dd, J=1.3, 8.3 Hz, 1H), 6.40-4.40 (s, 2H), 4.00 (t, J=6.9 Hz, 1H), 3.39-3.34 (m, 6H), 2.82 (dd, J=6.4, 13.3 Hz, 1H), 2.70 (dd, J=7.4, 13.1 Hz, 1H), 2.37-2.27 (m, 2H), 2.27-2.18 (m, 1H), 2.15-2.07 (m, 1H).	Rt = 2.15 min, m/z 500.2 [M+H] ⁺ (Method 1)

Example 131**Step A****4-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (Intermediate 131A-a)**

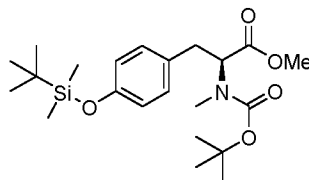
5 4-Bromo-7-azaindole (5.0 g, 28.90 mmol) was dissolved in DMF (40 mL) and the solution was stirred at RT under a stream of nitrogen. Sodium hydride (60% on mineral oil, 1.50 g, 37.58 mmol) was added portion wise and the reaction was stirred for 30 min. A solution of 4-toluenesulfonyl chloride (5.77 g, 30.37 mmol) in DMF (10 mL) was added dropwise over 10 min, and then the reaction was stirred for a further 2 h. The reaction mixture was carefully poured into cold water (100 mL) and stirred for 30 min. The resulting precipitate was collected by filtration and dried *in vacuo*. The product was obtained as an off-white solid (9.12 g).

LCMS (Method 6): $R_t = 1.59$ min, m/z 351.1/353.1 $[M+H]^+$

Step B**Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (Intermediate 131B)**

15 A solution of Intermediate 1B-c (500 mg, 1.69 mmol), tert-butyldimethylsilyl chloride (306 mg, 2.03 mmol) and imidazole (288 mg, 5.25 mmol) in DMF (10 mL) was stirred at RT for 18 h. The reaction mixture was partitioned between ethyl acetate (15 mL) and water (15 mL) and the organic layer was separated, washed with water (2 x 10 mL), dried (Na_2SO_4) and evaporated to give the desired product as a colourless oil (769 mg).

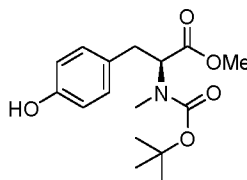
LCMS (Method 6): $R_t = 1.89$ min, m/z 432.4 $[M+\text{Na}]^+$

Step C

Methyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)phenyl)propanoate (Intermediate 131C)

5 Sodium hydride (72 mg, 1.80 mmol) was added to a solution of Intermediate 131B (692 mg, 1.69 mmol) in a mixture of THF (10 mL) and DMF (1 mL). After stirring for 10 min, methyl iodide (316 mg, 5.08 mmol) was added and stirring was continued for 24 h. The reaction mixture was partitioned between ethyl acetate (5 mL) and water (5 mL) and the organic layer was separated, washed with water (2 x 10 mL), dried (Na₂SO₄) and
 10 evaporated. The product was purified on a Si cartridge (25 g) eluting with 0-25% ethyl acetate in cyclohexane to give the desired product as a yellow oil (436 mg).

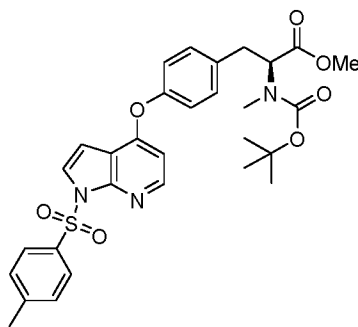
LCMS (Method 6): Rt = 1.95 min, m/z 424.3 [M+H]⁺

Step D

15 **Methyl N-(tert-butoxycarbonyl)-N-methyl-L-tyrosinate (Intermediate 131D)**

A solution of Intermediate 131C (436 mg, 1.03 mmol) in a mixture of acetic acid (4.45 mL), THF (1.5 mL) and water (1.5 mL) was stirred at RT for 18 h and then at 40°C for 18 h and at 75°C for 18 h. The reaction mixture was concentrated *in vacuo* and the pH adjusted to pH10 by the careful addition of solid potassium carbonate. The product was
 20 extracted into ethyl acetate (15 mL) and the organic layer was dried (Na₂SO₄) and evaporated. The product was purified on a Si cartridge (25 g) eluting with 0-25% ethyl acetate in cyclohexane to give the desired product as a colourless oil which crystallized on standing (110 mg).

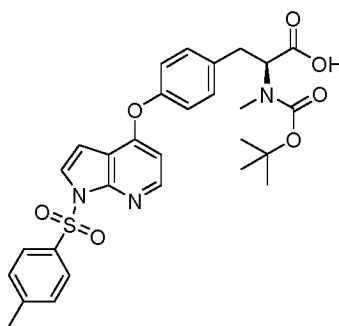
LCMS (Method 9): Rt = 2.95 min, m/z 332.2 [M+Na]⁺

Step E

Methyl (S)-2-((tert-butoxycarbonyl)(methyl)amino)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 131E-a)

5 Intermediate 131E-a was prepared from Intermediate 131A-a and Intermediate 131D using a similar procedure to that used in Step D of Example 1.

LCMS (Method 9): $R_t = 4.18$ min, m/z 580.1 $[M+H]^+$

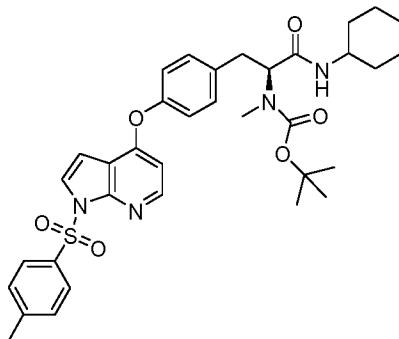
Step F

10 **(S)-2-((tert-Butoxycarbonyl)(methyl)amino)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 131F-a)**

Intermediate 131F-a was prepared from Intermediate 131E-a using a similar procedure to that used in Step E of Example 1.

LCMS (Method 9): $R_t = 3.77$ min, m/z 566.1 $[M+H]^+$

15 **Step G**

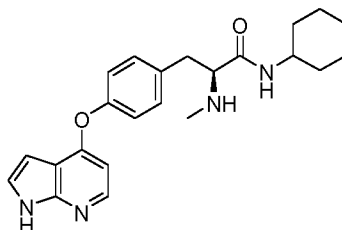


tert-Butyl (S)-(1-(cyclohexylamino)-1-oxo-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-2-yl)(methyl)carbamate (Intermediate 131G-a)

Intermediate 131G-a was prepared from Intermediate 131F-a and cyclohexylmethanamine using a similar procedure to that used in Step F of Example 1.

5 LCMS (Method 9): $R_t = 4.39$ min, m/z 647.2 $[M+H]^+$

Step H



(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-(methylamino)propanamide (Example 131)

10 Intermediate 131G-a (118 mg, 0.182 mmol) was dissolved in a mixture of DCM (4 mL) and TFA (4 mL) and the solution was stirred at RT for 1 h. The mixture was poured onto an SCX-2 cartridge (10 g). After flushing with methanol, the product was eluted with 2M methanolic ammonia and the volatiles were evaporated. The residue was dissolved in dioxane (4 mL) and 4M sodium hydroxide (4 mL) was added. The mixture was stirred at
15 80°C for 4 h. The reaction mixture was diluted with DCM/IPA (10:1) (10 mL) and washed with brine. The aqueous was extracted further with DCM (3 x 10 mL) and the combined extracts were dried (Na_2SO_4) and evaporated. The product was purified by HPLC eluting with a gradient of 0-80% acetonitrile in water (0.1% NH_4OH added) to give a white solid (27 mg).

20 $R_t = 2.47$ min, m/z 393.3 $[M+H]^+$ (Method 1)

^1H NMR (400 MHz, d_6 -DMSO) δ 11.72 (s, 1H), 8.05 (d, $J=5.4$ Hz, 1H), 7.58 (d, $J=8.1$ Hz, 1H), 7.34 (dd, $J=2.6, 3.3$ Hz, 1H), 7.25 (d, $J=8.6$ Hz, 2H), 7.06 (d, $J=8.6$ Hz, 2H), 6.36 (d, $J=5.4$ Hz, 1H), 6.21 (dd, $J=1.9, 3.5$ Hz, 1H), 3.57-3.47 (m, 1H), 3.10 (t, $J=6.9$ Hz, 1H), 2.76 (d, $J=6.9$ Hz, 2H), 2.18 (s, 3H), 1.87 (s, 1H), 1.69-1.48 (m, 4H), 1.29-0.99 (m,
25 6H).

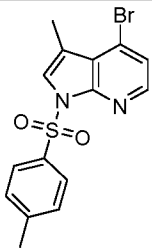
$$ee\% = 38\%$$

Examples 132 to 144

The following Examples were prepared in a similar way to Example 131 by replacing at each step the suitable starting materials.

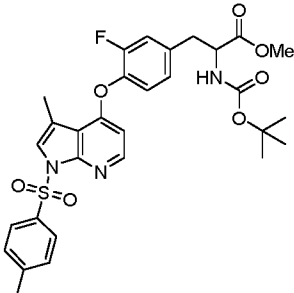
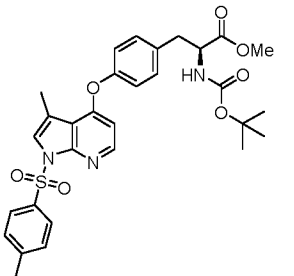
5 Preparation of Intermediate 131A-b

The following intermediate was prepared in a similar manner to Intermediate 131A-a from the indicated starting material.

Intermediate	Structure	Starting materials	LC-MS
131A-b		4-Bromo-3-methyl-7-azaindole	Rt = 1.71 min, m/z 365.0/367.0 [M+H] ⁺ (Method 6)

Preparation of Intermediates from 131E-b to 131E-e

10 The following intermediates were prepared in a similar manner to Intermediate 131E-a from the indicated starting materials according to the method used in Step D of Example 1.

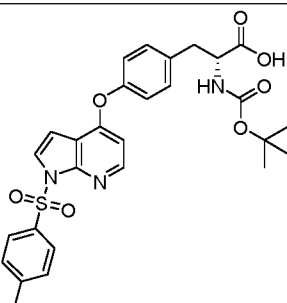
Intermediate	Structure	Starting materials	LC-MS
131E-b		131A-b and 1B-b	Rt = 1.74 min, m/z 598.2 [M+H] ⁺ (Method 6)
131E-c		131A-b and 1B-c	Rt = 1.79 min, m/z 580.2 [M+H] ⁺ (Method 6)

Intermediate	Structure	Starting materials	LC-MS
131E-d		131A-b and 1B-d	Rt = 1.79 min, m/z 580.2 [M+H] ⁺ (Method 6)
131E-e		131A-a and 1B-d	Rt = 4.03 min, m/z 566.1 [M+H] ⁺ (Method 9)

Preparation of Intermediates from 131F-b to 131F-e

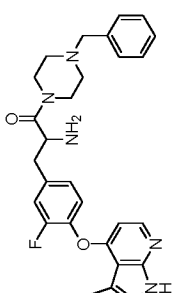
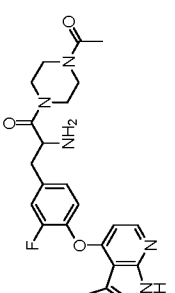
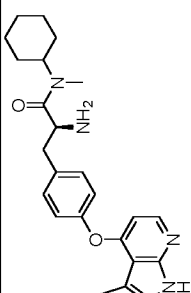
The following intermediates were prepared from the indicated starting materials according to the method used in Step E of Example 1.

Intermediate	Structure	Starting materials	LC-MS
131F-b		131E-b	Rt = 1.71 min, m/z 584.2 [M+H] ⁺ (Method 6)
131F-c		131E-c	Rt = 1.69 min, m/z 566.2 [M+H] ⁺ (Method 6)
131F-d		131E-d	Rt = 1.68 min, m/z 566.2 [M+H] ⁺ (Method 6)

Intermediate	Structure	Starting materials	LC-MS
131F-e		131E-e	Rt = 3.68 min, m/z 552.1 [M+H] ⁺ (Method 9)

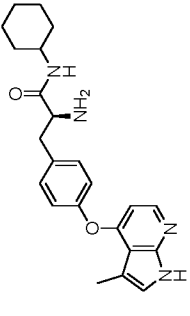
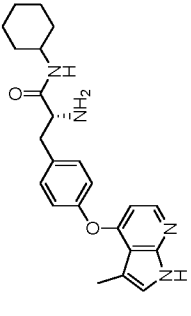
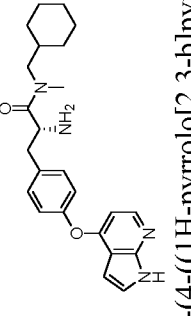
Preparation of Examples

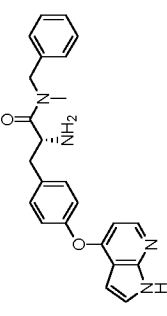
The following examples were prepared using the same synthetic sequence as for Example 131, by replacing in Step G the indicated Intermediate 131F and an amine.

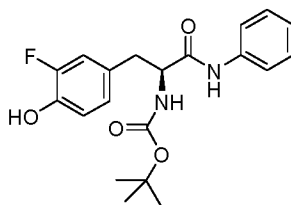
Ex	Structure	Intermediate 131F / Amine	¹ H NMR	LC-MS
132	 2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	131F-b / 1-benzyl-piperazine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.41 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.34-7.22 (m, 7H), 7.16-7.13 (m, 1H), 7.10 (dd, J=1.4, 8.2 Hz, 1H), 6.16 (d, J=5.4 Hz, 1H), 3.96-3.91 (m, 1H), 3.54-3.46 (m, 1H), 3.43 (s, 2H), 3.42-3.29 (m, 3H), 2.79 (dd, J=6.5, 13.1 Hz, 1H), 2.68 (dd, J=7.0, 13.3 Hz, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.38-2.30 (m, 2H), 2.21-2.12 (m, 1H), 2.05-1.96 (m, 1H), 1.77-1.76 (m, 2H).	Rt = 2.11 min, m/z 488.4 [M+H] ⁺ (Method 1)
133	 1-(4-acetylpiperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	131F-b / 1-(piperazin-1-yl)ethan-1-one	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.96 (d, J=5.4 Hz, 1H), 7.34 (dd, J=1.7, 11.9 Hz, 1H), 7.27- 7.20 (m, 1H), 7.15-7.10 (m, 2H), 6.14- 6.09 (m, 1H), 3.98-3.93 (m, 1H), 3.50- 3.37 (m, 6H), 3.21-3.17 (m, 1H), 2.83 (dd, J=6.1, 13.3 Hz, 1H), 2.69 (dd, J=7.5, 13.2 Hz, 1H), 2.61 – 2.51 (m, 1H), 2.37 (d, J=0.9 Hz, 3H), 2.01 (s, 3H), 1.77-1.77 (m, 2H).	Rt = 2.07 min, m/z 440.3 [M+H] ⁺ (Method 1)
134	 (S)-2-amino-N-cyclohexyl-N-methyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	131F-c / N-methylcyclohexan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.36 (s, 1H), 7.99 (dd, J=1.8, 5.4 Hz, 1H), 7.28-7.23 (m, 2H), 7.13-7.10 (m, 1H), 7.07-7.01 (m, 2H), 6.22 (dd, J=5.4, 10.9 Hz, 1H), 4.27-4.16 & 3.51-3.40 (2xm, 1H), 3.90-3.80 (m, 1H), 2.79-2.67 (m, 2H), 2.65 (d, J=1.8 Hz, 3H), 2.33-2.31 (m, 3H), 1.77-1.22 (m, 10H), 1.20-0.95 (m, 2H).	Rt = 2.68 min, m/z 407.3 [M+H] ⁺ (Method 1)

Ex	Structure	Intermediate ¹³ 1F / Amine	¹ H NMR	LC-MS
135	(S)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (ee% = 79%)	131F-c / benzylamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.35 (s, 1H), 8.32 (t, J=6.0 Hz, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.28-7.12 (m, 8H), 7.04 (d, J=8.5 Hz, 2H), 6.23 (d, J=5.4 Hz, 1H), 4.34-4.19 (m, 2H), 3.46 (dd, J=5.9, 7.5 Hz, 1H), 2.94 (dd, J=5.7, 13.3 Hz, 1H), 2.72 (dd, J=7.6, 13.3 Hz, 1H), 2.34 (d, J=1.1 Hz, 3H), 1.92 (s, 2H).	Rt = 2.48 min, m/z 401.2 [M+H] ⁺ (Method 1)
136	(R)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (ee% = 72%)	131F-d / benzylamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.37 (s, 1H), 8.32 (t, J=6.0 Hz, 1H), 7.99 (d, J=5.5 Hz, 1H), 7.32-7.09 (m, 8H), 7.06-7.02 (m, 2H), 6.23 (d, J=5.4 Hz, 1H), 4.35-4.19 (m, 2H), 3.46 (dd, J=6.0, 7.4 Hz, 1H), 2.94 (dd, J=5.8, 13.3 Hz, 1H), 2.72 (dd, J=7.6, 13.3 Hz, 1H), 2.34 (d, J=1.0 Hz, 3H), 1.80 (s, 2H).	Rt = 2.50 min, m/z 401.2 [M+H] ⁺ (Method 1)
137	(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide	131F-c / aniline	¹ H NMR (400 MHz, d6-DMSO) δ 11.34 (s, 1H), 9.84 (s, 1H), 7.95 (d, J=5.4 Hz, 1H), 7.60-7.58 (m, 2H), 7.34-7.28 (m, 4H), 7.13-7.08 (m, 1H), 7.05 (d, J=23.5 Hz, 3H), 6.17 (d, J=5.4 Hz, 1H), 3.60 (dd, J=5.9, 7.7 Hz, 1H), 3.01 (dd, J=5.7, 13.4 Hz, 2H), 2.79 (dd, J=7.6, 13.0 Hz, 2H), 2.31-2.30 (m, 3H).	Rt = 2.47 min, m/z 387.2 [M+H] ⁺ (Method 1)

Ex	Structure	Intermediate ¹³ 1F / Amine	¹ H NMR	LC-MS
138	(R)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)-N-phenylpropanamide (ee% = 80%)	Intermediate ¹³ 1F-d / aniline	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.34 (s, 1H), 9.79 (s, 1H), 7.95 (d, J=5.4 Hz, 1H), 7.61-7.58 (m, 2H), 7.34-7.27 (m, 4H), 7.12-7.09 (m, 1H), 7.08-7.01 (m, 3H), 6.17 (d, J=5.4 Hz, 1H), 3.58 (dd, J=5.7, 7.8 Hz, 1H), 3.00 (dd, J=5.7, 13.3 Hz, 1H), 2.77 (dd, J=7.9, 13.3 Hz, 1H), 2.31 (d, J=1.0 Hz, 3H), 2.00-1.94 (s, 2H).	Rt = 2.47 min, m/z 387.2 [M+H] ⁺ (Method 1)
139	(S)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)propanamide (ee% = 76%)	¹³ 1F-c / cyclohexylmethan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.33 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.74 (t, J=5.9 Hz, 1H), 7.26 (d, J=8.5 Hz, 2H), 7.11 (dd, J=1.1, 2.1 Hz, 1H), 7.05 (d, J=8.5 Hz, 2H), 6.22 (d, J=5.4 Hz, 1H), 3.39 (t, J=6.7 Hz, 1H), 2.97-2.77 (m, 3H), 2.69 (dd, J=7.2, 13.4 Hz, 1H), 2.33 (d, J=1.0 Hz, 3H), 1.74 (s, 2H), 1.66-1.49 (m, 5H), 1.35-1.23 (m, 1H), 1.15-1.07 (m, 3H), 0.90-0.68 (m, 2H).	Rt = 2.73 min, m/z 407.3 [M+H] ⁺ (Method 1)
140	(R)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yloxy)phenyl)propanamide (ee% = 71%)	¹³ 1F-d / cyclohexylmethan-amine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.35 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.75 (t, J=5.9 Hz, 1H), 7.26 (d, J=8.5 Hz, 2H), 7.11 (dd, J=1.2, 2.2 Hz, 1H), 7.05 (d, J=8.5 Hz, 2H), 6.22 (d, J=5.4 Hz, 1H), 3.43-3.37 (m, 1H), 2.97-2.76 (m, 4H), 2.69 (dd, J=7.3, 13.2 Hz, 1H), 2.33 (d, J=1.0 Hz, 3H), 1.66-1.53 (m, 6H), 1.32-1.07 (m, 4H), 0.84-0.71 (m, 2H).	Rt = 2.74 min, m/z 407.3 [M+H] ⁺ (Method 1)

Ex	Structure	Intermediate 131F / Amine	¹ H NMR	LC-MS
141	 (S)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (ee% = 76%)	131F-c / cyclo-hexanamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.36 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.57 (d, J=8.1 Hz, 1H), 7.26 (d, J=8.6 Hz, 2H), 7.13 – 7.09 (m, 1H), 7.04 (d, J=8.6 Hz, 2H), 6.23 (d, J=5.4 Hz, 1H), 3.54-3.45 (m, 1H), 2.85 (dd, J=5.9, 13.3 Hz, 1H), 2.67 (dd, J=7.4, 13.3 Hz, 1H), 2.32 (d, J=1.0 Hz, 3H), 2.06-2.05 (s, 2H), 1.68-1.49 (m, 5H), 1.30-1.00 (m, 6H).	Rt = 2.58 min, m/z 393.3 [M+H] ⁺ (Method 1)
142	 (R)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (ee% = 72%)	131F-d / cyclo-hexanamine	¹ H NMR (400 MHz, d6-DMSO) δ 11.35 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.57 (d, J=8.1 Hz, 1H), 7.26 (d, J=8.6 Hz, 2H), 7.12 (dd, J=1.2, 2.1 Hz, 1H), 7.04 (d, J=8.5 Hz, 2H), 6.23 (d, J=5.4 Hz, 1H), 3.53-3.45 (m, 1H), 3.29 – 3.33 (m, 1H), 2.85 (dd, J=5.9, 13.2 Hz, 1H), 2.67 (dd, J=7.5, 13.2 Hz, 1H), 2.32 (d, J=1.0 Hz, 3H), 1.80 (s, 2H), 1.69-1.49 (m, 6H), 1.29-1.01 (m, 4H).	Rt = 2.59 min, m/z 393.2 [M+H] ⁺ (Method 1)
143	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide	131F-e / cyclohexyl-N-methylmethan-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.72 (s, 1H), 8.08 – 8.05 (m, 1H), 7.36-7.32 (m, 1H), 7.28 (dd, J=8.4, 16.1 Hz, 2H), 7.09-7.05 (m, 2H), 6.38-6.35 (m, 1H), 6.19-6.16 (m, 1H), 3.90-3.76 (2 x t, 1H), 3.23 (dd, J=7.2, 13.1 Hz, 1H), 2.99-2.92 (m, 1H), 2.87 and 2.77 (2 x s, 3H), 2.86- 2.78 (m, 1H), 2.71-2.61 (m, 1H), 1.92 (m, 2H), 1.63-1.42 (m, 6H), 1.17- 1.05 (m, 3H), 0.90-0.75 (m, 2H).	Rt = 2.78 min, m/z 407.3 [M+H] ⁺ (Method 1)

Ex	Structure	Intermediate 131F / Amine	¹ H NMR	LC-MS
144	 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-L-methylpropanamide	Intermediate 131F / Amine 131F-e / N-methyl-L-phenylmethan-amine	¹ H NMR (400 MHz, d6-DMSO) δ 11.72 (s, 1H), 8.08-8.05 (m, 1H), 7.35-7.19 (m, 6H), 7.14-7.03 (m, 4H), 6.40-6.34 (m, 1H), 6.20-6.17 (m, 1H), 4.63-4.33 (m, 2H), 4.00- 3.80 (2 x t, 1H), 2.87 (dd, J=7.0, 13.1 Hz, 1H), 2.83-2.76 (2 x s, 3H), 2.76- 2.63 (m, 1H), 1.84 (s, 2H).	LC-MS Rt = 2.48 min, m/z 401.2 [M+H] ⁺ (Method 1)

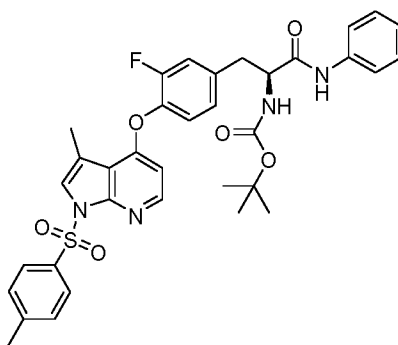
Example 145**Step A**

tert-Butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-hydroxyphenyl)propanoate (Intermediate 145A-a)

Intermediate 145A-a was prepared from (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-hydroxyphenyl)propanoic acid and aniline using a similar procedure to that used for Step F of Example 1.

LCMS (Method 6): $R_t = 1.36$ min, m/z 373.1 $[M-H]^-$

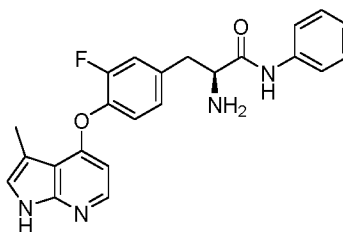
Step B



tert-Butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-(3-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 145B-a)

Intermediate 145B-a was prepared from Intermediate 145A-a and 131A-b using a similar procedure to that used for Step D of Example 1.

LCMS (Method 6): $R_t = 1.80$ min, m/z 659.3 $[M+H]^+$

Step C

(S)-2-amino-3-(3-(3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenylpropan-1-amine

yl)oxy)phenyl)-N-phenylpropanamide (Example 145)

Intermediate 145B-a (180 mg, 0.274 mmol) was dissolved in DCM (5 mL) and TFA (1 mL) was added. After stirring at RT for 90 min the volatiles were evaporated and the residue was dissolved in methanol. The solution was loaded onto an SCX-2 cartridge (5 g).
 5 After flushing with DCM and methanol, the free base was eluted with 2M methanolic ammonia. Evaporation gave a residue which was re-dissolved in methanol (5 mL). Lithium hydroxide hydrate (22 mg, 0.516 mmol) in water (2 mL) was added and the reaction was stirred at RT for 18 h then at 50°C for 2 h. The methanol was evaporated and the aqueous mixture was extracted with DCM (12 mL). The organic was dried (Na₂SO₄) and
 10 evaporated. The product was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH₄OH) to give a white solid (14 mg).

Rt = 2.62 min, m/z 405.2 [M+H]⁺ (Method 1)

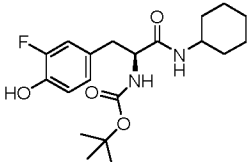
¹H NMR (400 MHz, d₆-DMSO) δ 11.38 (s, 1H), 9.84 (s, 1H), 7.94 (d, J=5.4 Hz, 1H), 7.60 (d, J=7.5 Hz, 2H), 7.36-7.12 (m, 6H), 7.05 (t, J=7.4 Hz, 1H), 6.08 (d, J=4.9 Hz, 1H),
 15 1H), 3.60 (dd, J=5.7, 7.9 Hz, 1H), 3.01 (dd, J=5.5, 13.4 Hz, 1H), 2.79 (dd, J=8.1, 13.4 Hz, 1H), 2.37 (d, J=1.0 Hz, 3H), 2.00 (s, 2H).

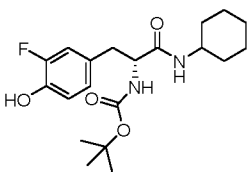
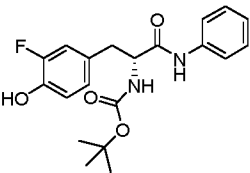
Examples 146 to 149

The following Examples were prepared in a similar way to Example 145 by replacing at each step the suitable starting materials.

20 Preparation of Intermediates 145A-b to 145A-d

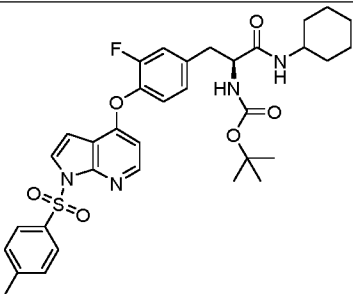
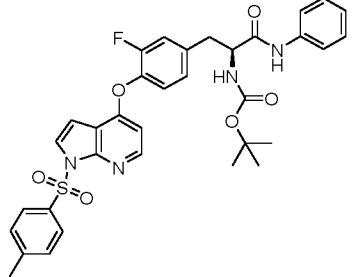
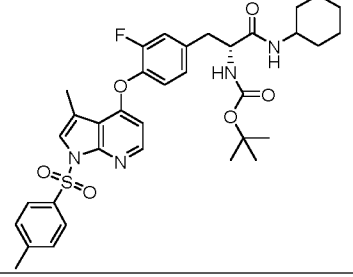
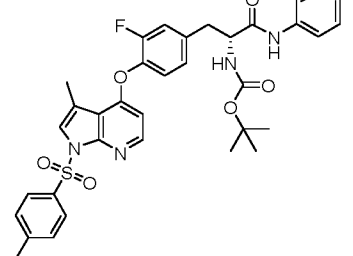
The following intermediates were prepared in a similar manner to Intermediate 145A-a by replacing in Step A of Example 145 the tyrosine with the indicated amine.

Intermediate	Structure	Starting material	LC-MS
145A-b		3-Fluoro-L-tyrosine and cyclohexylamine	Rt = 3.33 min, m/z 381.1 [M+H] ⁺ (Method 7)

Intermediate	Structure	Starting material	LC-MS
145A-c		3-Fluoro-D-tyrosine and cyclohexanamine	Rt = 1.15 min, m/z 379.3 [M-H] ⁻ (Method 6)
145A-d		3-Fluoro-D-tyrosine and aniline	Rt = 1.41 min, m/z 373.2 [M-H] ⁻ (Method 6)

Preparation of Intermediates from 145B-b to 145B-e

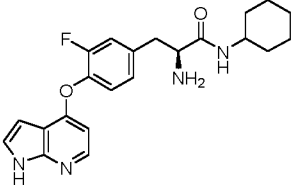
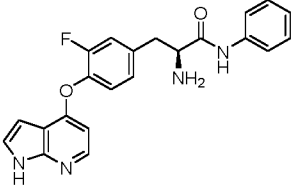
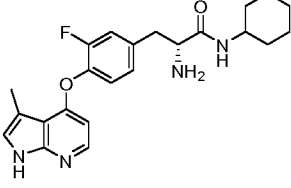
The following intermediates were prepared in a similar manner to Intermediate 145B-a from the indicated starting materials.

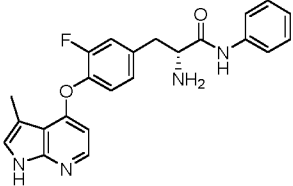
Intermediate	Structure	Starting materials	LC-MS
145B-b		145A-b and 131A-a	Rt = 1.75 min, m/z 651.3 [M+H] ⁺ (Method 6)
145B-c		145A-a and 131A-a	Rt = 1.73 min, m/z 645.2 [M+H] ⁺ (Method 6)
145B-d		145A-c and 131A-b	Rt = 1.79 min, m/z 665.3 [M+H] ⁺ (Method 6)
145B-e		145A-d and 131A-b	Rt = 1.77 min, m/z 659.2 [M+H] ⁺ (Method 6)

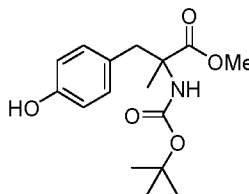
Preparation of Examples

The following examples were prepared in a similar manner to Example 145, following the same synthetic sequence, by replacing in Step C the indicated Intermediate in the table below.

5

Ex	Structure	Intermediate	¹ H NMR	LC-MS
146	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-cyclohexylpropanamide	145B -b	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.76 (s, 1H), 8.05 (d, J=5.4 Hz, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.37 (dd, J=2.1, 3.2 Hz, 1H), 7.29-7.24 (m, 2H), 7.11-7.07 (m, 1H), 6.33 (d, J=5.5 Hz, 1H), 6.28-6.24 (m, 1H), 3.56-3.47 (m, 1H), 3.38 (t, J=6.7 Hz, 1H), 2.87 (dd, J=6.0, 13.2 Hz, 1H), 2.76-2.67 (m, 1H), 1.77 (s, 2H), 1.70-1.57 (m, 4H), 1.30-1.04 (m, 6H).	R _t = 2.50 min, m/z 397.2 [M+H] ⁺ (Method 3)
147	 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-phenylpropanamide	145B -c	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.74 (s, 1H), 9.82 (s, 1H), 8.02 (d, J=5.3 Hz, 1H), 7.60 (dd, J=1.1, 8.6 Hz, 2H), 7.37-7.24 (m, 5H), 7.15 (dd, J=1.5, 8.3 Hz, 1H), 7.05 (tt, J=1.2, 7.4 Hz, 1H), 6.28 (dd, J=0.4, 5.4 Hz, 1H), 6.20 (dd, J=1.9, 3.4 Hz, 1H), 3.61 (t, J=6.9 Hz, 1H), 3.01 (dd, J=5.7, 13.3 Hz, 1H), 2.81 (dd, J=8.0, 13.4 Hz, 1H), 2.01 (s, 2H).	R _t = 2.41 min, m/z 391.2 [M+H] ⁺ (Method 1)
148	 (R)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	145B -d	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.60 (d, J=8.1 Hz, 1H), 7.28-7.20 (m, 2H), 7.15-7.06 (m, 2H), 6.15 (d, J=4.8 Hz, 1H), 3.55-3.46 (m, 1H), 3.38 (t, J=6.7 Hz, 1H), 2.86 (dd, J=6.0, 13.2 Hz, 1H), 2.71 (dd, J=7.3, 13.0 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 1.77 (d, J=1.2 Hz, 2H), 1.69-1.52 (m, 5H), 1.29-1.16 (m, 2H), 1.15-1.02 (m, 3H).	R _t = 2.71 min, m/z 411.2 [M+H] ⁺ (Method 1)

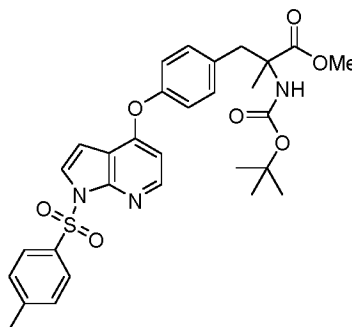
Ex	Structure	Intermediate	¹ H NMR	LC-MS
149	 (R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide	145B -e	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.38 (s, 1H), 9.84 (s, 1H), 7.94 (d, J=5.4 Hz, 1H), 7.60 (d, J=7.5 Hz, 2H), 7.36-7.12 (m, 6H), 7.05 (t, J=7.4 Hz, 1H), 6.08 (d, J=4.9 Hz, 1H), 3.60 (dd, J=5.7, 7.9 Hz, 1H), 3.01 (dd, J=5.5, 13.4 Hz, 1H), 2.79 (dd, J=8.1, 13.4 Hz, 1H), 2.37 (d, J=1.0 Hz, 3H), 2.00 (s, 2H).	R _t = 2.62 min, m/z 405.2 [M+H] ⁺ (Method 1)

Example 150**Step A****Methyl 2-((tert-butoxycarbonyl)amino)-3-(4-hydroxyphenyl)-2-****5 methylpropanoate (Intermediate 150A)**

Intermediate 150A was prepared from 2-amino-3-(4-hydroxyphenyl)-2-methylpropanoic acid using similar procedures to those used for Steps A and B of Example 1.

LCMS (Method 6): R_t = 1.27 min, m/z 332.1 [M+Na]⁺

10

Step B

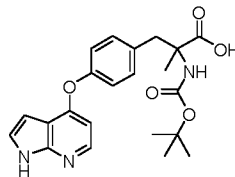
Methyl 2-((tert-butoxycarbonyl)amino)-2-methyl-3-(4-((1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 150B)

Intermediate 150B was prepared from Intermediate 150A and Intermediate 131A-a

using a similar procedure to that used for Step D of Example 1.

LCMS (Method 6): $R_t = 1.73$ min, m/z 580.2 $[M+H]^+$

Step C

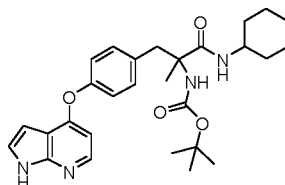


5 **3-(4-((1H-Pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-((tert-butoxycarbonyl)-amino)-2-methylpropanoic acid (Intermediate 150C)**

Intermediate 150B (1.0 g, 1.73 mmol) was dissolved in methanol (10 mL) and 2M lithium hydroxide (1 mL) was added. The reaction was stirred at 60°C for 3 h. A further portion of 2M lithium hydroxide (1 mL) was added and heating was continued for 4 h. After stirring at RT for a further 18 h, the reaction mixture was evaporated, treated with 1M hydrochloric acid (20 mL) and the product extracted with DCM (30 mL). The organic extract was dried (Na_2SO_4) and evaporated to give the product as a gum (861 mg).

LCMS (Method 6): $R_t = 1.13$ min, m/z 412.3 $[M+H]^+$

Step D

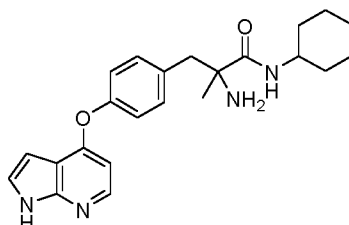


15 **tert-Butyl (3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-2-methyl-1-oxopropan-2-yl)carbamate (Intermediate 150D)**

Intermediate 150D was prepared from Intermediate 150C and cyclohexanamine using a method similar to that used in Steps F of Example 1.

LCMS (Method 6): $R_t = 1.45$ min, m/z 493.2 $[M+H]^+$ (Method 1)

Step D



3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-2-methylpropanamide (Example 150)

Example 150 was prepared from Intermediate 150D using a method similar to that used in Step G of Example 1.

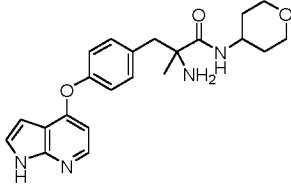
5 LCMS (Method 1): $R_t = 2.47$ min, m/z 393.3 $[M+H]^+$

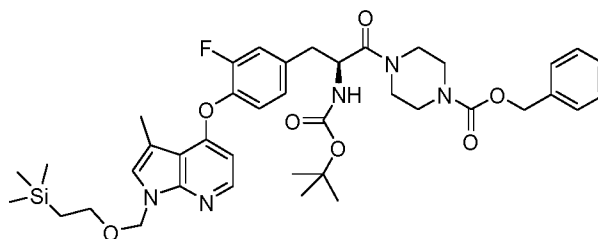
1H NMR (400 MHz, d_6 -DMSO) δ 11.71 (s, 1H), 8.05 (d, $J=5.4$ Hz, 1H), 7.47 (d, $J=8.3$ Hz, 1H), 7.35-7.32 (m, 1H), 7.23 (d, $J=8.6$ Hz, 2H), 7.06 (d, $J=8.6$ Hz, 2H), 6.37 (d, $J=5.4$ Hz, 1H), 6.19 (dd, $J=2.0, 3.5$ Hz, 1H), 3.51-3.43 (m, 1H), 3.05 (d, $J=12.8$ Hz, 1H), 2.63 (d, $J=12.8$ Hz, 1H), 1.80 (s, 2H), 1.70-1.47 (m, 5H), 1.34-1.22 (m, 2H), 1.21 (s, 3H),
10 1.19-0.98 (m, 3H).

Preparation of Example 151

Example 151 was prepared from Intermediate 150C in a similar manner to Example 150, following the same synthetic sequence, by replacing in Step D the indicated amine starting material the table below.

15

Ex	Structure	Amine	1H NMR	LC-MS
151	 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-2-methyl-N-(tetrahydro-2H-pyran-4-yl)propanamide	Tetrahydro-2H-pyran-4-amine	1H NMR (400 MHz, d_6 -DMSO) δ 11.71 (s, 1H), 8.05 (d, $J=5.4$ Hz, 1H), 7.57 (d, $J=8.1$ Hz, 1H), 7.34 (dd, $J=2.0, 3.2$ Hz, 1H), 7.23 (d, $J=8.6$ Hz, 2H), 7.07 (d, $J=8.6$ Hz, 2H), 6.38 (d, $J=5.4$ Hz, 1H), 6.18 (dd, $J=1.3, 3.4$ Hz, 1H), 3.82-3.66 (m, 3H), 3.36-3.26 (m, 2H), 3.05 (d, $J=12.8$ Hz, 1H), 2.66-2.61 (m, 1H), 1.79 (s, 2H), 1.63-1.24 (m, 4H), 1.22 (s, 3H).	$R_t = 1.89$ min, m/z 395.2 $[M+H]^+$ (Method 1)

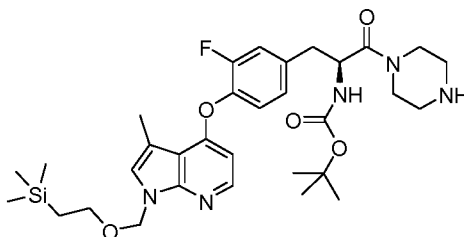
Example 152**Step A**

5 **Benzyl (S)-4-(2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazine-1-carboxylate (Intermediate 152A)**

Intermediate 152A was prepared from 1E-a and benzyl piperazine-1-carboxylate using a method similar that used in Step F of Example 1.

LCMS (Method 6): $R_t = 1.89$ min, m/z 762.2 $[M+H]^+$

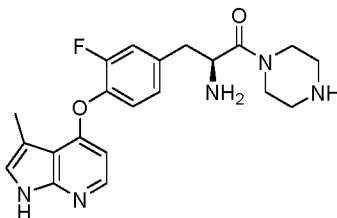
10 **Step B**



tert-Butyl (S)-(3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-(piperazin-1-yl)propan-2-yl)carbamate (Intermediate 152B)

15 Intermediate 152A (1.50 g, 1.97 mmol) was dissolved in IMS (44.6 mL) and 10% palladium on carbon (187 mg) was added. The mixture was stirred under an atmosphere of hydrogen gas provided by a balloon. After 18 h, the mixture was filtered through Celite[®] and the solvent was evaporated *in vacuo*. The residue was chromatographed on a 40 g Si cartridge eluting with 0-10% 2M ammonia in methanol in DCM. The product was obtained
20 as a white solid (951 mg).

LCMS (Method 6): $R_t = 1.39$ min, m/z 628.2 $[M+H]^+$

Step C

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperazin-1-yl)propan-1-one (Example 152)

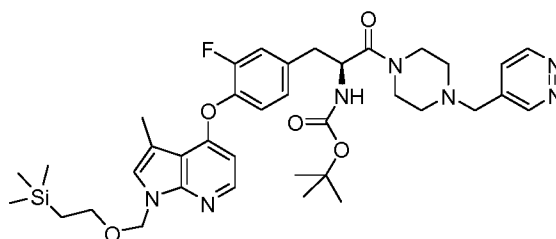
Intermediate 152B (66 mg, 0.11 mmol) was dissolved in DCM (1.2 mL) and TFA (1.2 mL) was added. The solution was stirred at RT for 3 h. The reaction mixture was diluted with methanol and passed down a 5 g SCX-2 cartridge. After flushing with methanol, the product was eluted with 2M ammonia in methanol. Evaporation gave a residue which was dissolved in THF (1.2 mL). 4M aqueous sodium hydroxide (1.2 mL) was added and the reaction was stirred at RT for 1 h. After diluting with water (8 mL), the product was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and evaporated. The product was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH₄OH added). The desired product was obtained as a beige solid (23 mg).

LCMS (Method 1): Rt = 1.57 min, m/z 398.2 [M+H]⁺

¹H NMR (400 MHz, d₆-DMSO) δ 11.39 (s, 1H), 8.00-7.96 (m, 1H), 7.34-7.20 (m, 2H), 7.15-7.08 (m, 2H), 6.16-6.10 (m, 1H), 3.96-3.89 (m, 1H), 3.50-3.30 (m, 8H), 2.80 (dd, J=6.2, 13.2 Hz, 1H), 2.72-2.63 (m, 2H), 2.55-2.52 (m, 1H), 2.38-2.36 (m, 4H).

ee% (n.d.)

Example 153

Step A

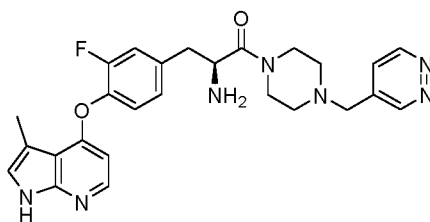
tert-Butyl (S)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperazin-1-yl)propan-1-one

1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-(4-(pyridazin-4-ylmethyl)piperazin-1-yl)propan-2-yl)carbamate (Intermediate 153A)

A solution of Intermediate 152B (150 mg, 0.24 mmol), pyridazine-4-carbaldehyde (39 mg, 0.36 mmol), and acetic acid (0.05 mL) in DCE (3 mL) was stirred at RT over 4 Å molecular sieves for 2.5 h. Sodium triacetoxyborohydride (127 mg, 0.60 mmol) was added and stirring was continued for a further 1 h. The mixture was diluted with methanol and passed through a 10g SCX-2 cartridge. After flushing with methanol, the product was eluted with 2M ammonia in methanol. Evaporation gave the desired product (168 mg) which was used without further purification.

LCMS (Method 6): $R_t = 1.69$ min, m/z 720.3 $[M+H]^+$

Step B



(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridazin-4-ylmethyl)piperazin-1-yl)propan-1-one (Example 153)

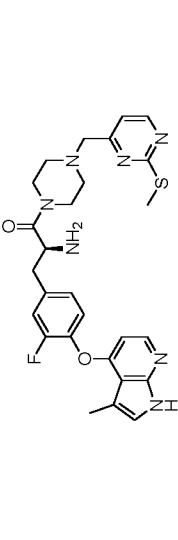
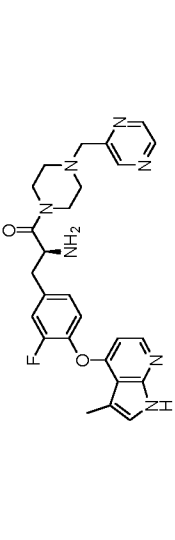
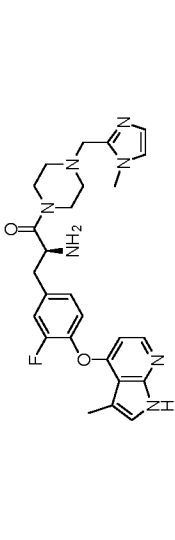
Example 153 was prepared from Intermediate 153A using a method similar to that used for Step G of Example 1.

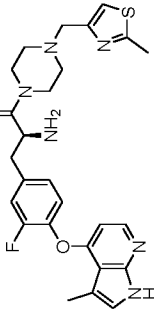
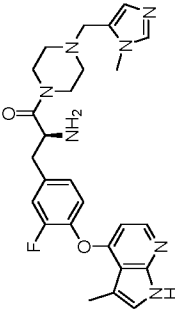
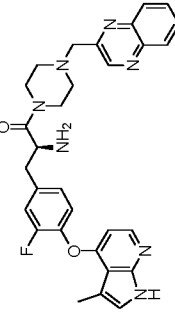
LCMS (Method 1): $R_t = 2.07$ min, m/z 490.1 $[M+H]^+$

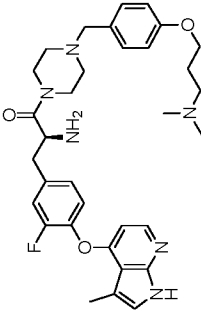
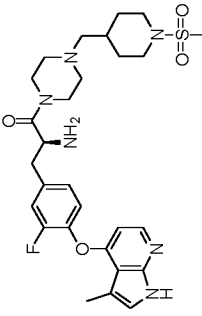
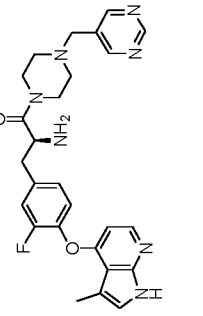
1H NMR (400 MHz, d_6 -DMSO) δ 11.40 (s, 1H), 9.18-9.15 (m, 2H), 7.99 (d, $J=5.4$ Hz, 1H), 7.59 (dd, $J=2.4, 5.1$ Hz, 1H), 7.32 (dd, $J=1.9, 11.8$ Hz, 1H), 7.24 (dd, $J=8.4, 8.4$ Hz, 1H), 7.14 (s, 1H), 7.11 (dd, $J=1.3, 8.3$ Hz, 1H), 6.17 (d, $J=5.4$ Hz, 1H), 3.93 (dd, $J=6.8, 6.8$ Hz, 1H), 3.55 (s, 2H), 3.53-3.36 (m, 4H), 2.80 (dd, $J=6.2, 13.2$ Hz, 1H), 2.67 (dd, $J=7.5, 13.2$ Hz, 1H), 2.43-2.22 (m, 6H), 2.18-2.10 (m, 1H), 1.63-1.83 (s, 2H).

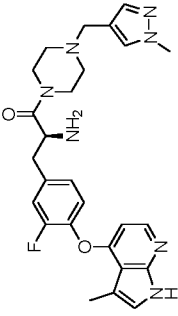
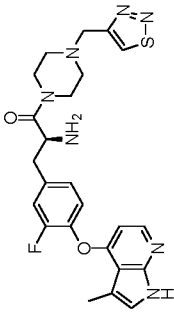
Examples 154 to 164

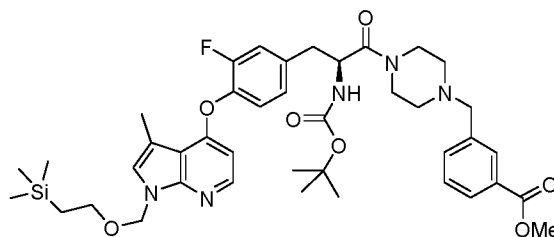
The following examples were prepared in a similar manner to Example 153 by replacing in Step A the corresponding aldehyde indicated in the table below.

Ex	Structure	Aldehyde	¹ H NMR	LC-MS
154	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-(methylthio)pyrimidin-4-yl)methyl)piperazin-1-yl)propan-1-one	2-(Methylthio)-pyrimidine-4-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.58 (d, J=5.1 Hz, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.32 (dd, J=1.9, 11.8 Hz, 1H), 7.27-7.21 (m, 2H), 7.15-7.09 (m, 2H), 6.17 (d, J=5.0 Hz, 1H), 3.95 (dd, J=6.9, 6.9 Hz, 1H), 3.54 (s, 3H), 3.51-3.38 (m, 3H), 2.80 (dd, J=6.4, 13.2 Hz, 1H), 2.72-2.64 (m, 1H), 2.46-2.42 (m, 5H), 2.39 (d, J=0.9 Hz, 3H), 2.34-2.22 (m, 1H), 2.20-2.10 (m, 1H), 1.75 (s, 2H).	Rt = 2.39 min, m/z 536.1 [M+H] ⁺ (Method 1)
155	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)propan-1-one	Pyrazine-2-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 8.69 (d, J=1.4 Hz, 1H), 8.59-8.54 (m, 2H), 7.99 (d, J=5.4 Hz, 1H), 7.31 (dd, J=1.8, 11.8 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.15-7.09 (m, 2H), 6.17 (d, J=5.2 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.65 (s, 2H), 3.50-3.36 (m, 4H), 2.80 (dd, J=6.4, 13.1 Hz, 1H), 2.68 (dd, J=7.3, 13.2 Hz, 1H), 2.47-2.41 (m, 2H), 2.39 (d, J=0.8 Hz, 3H), 2.34-2.25 (m, 1H), 2.19-2.10 (m, 1H), 1.74 (s, 2H).	Rt = 2.00 min, m/z 490.1 [M+H] ⁺ (Method 1)
156	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)propan-1-one	1-Methyl-1H-imidazole-2-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 8.01 (d, J=5.4 Hz, 1H), 7.31 (dd, J=2.0, 11.9 Hz, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.16-7.12 (m, 1H), 7.12-7.08 (m, 1H), 7.08 (d, J=1.1 Hz, 1H), 6.75 (d, J=1.2 Hz, 1H), 6.17 (d, J=4.9 Hz, 1H), 3.97-3.90 (m, 1H), 3.64 (s, 3H), 3.49 (s, 2H), 3.47-3.35 (m, 4H), 2.79 (dd, J=6.4, 13.2 Hz, 1H), 2.67 (dd, J=7.4, 13.2 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.37-2.33 (m, 2H), 2.24-2.14 (m, 1H), 2.10-2.04 (m, 1H), 1.72 (s, 2H).	Rt = 1.85 min, m/z 492.1 [M+H] ⁺ (Method 1)

Ex	Structure	Aldehyde	¹ H NMR	LC-MS
157	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-methylthiazol-4-yl)methyl)piperazin-1-yl)propan-1-one	2-Methylthiazole-4-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.39 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.31 (dd, J=2.1, 11.8 Hz, 1H), 7.24 (s, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.16-7.12 (m, 1H), 7.12-7.08 (m, 1H), 6.16 (d, J=4.8 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.51 (s, 2H), 3.50-3.34 (m, 4H), 2.79 (dd, J=6.4, 13.2 Hz, 1H), 2.67 (dd, J=7.3, 13.3 Hz, 1H), 2.62-2.62 (m, 3H), 2.45-2.40 (m, 1H), 2.39 (d, J=1.0 Hz, 3H), 2.34-2.24 (m, 1H), 2.18-2.07 (m, 1H), 1.73 (s, 2H).	Rt = 3.42 min, m/z 509.1 [M+H] ⁺ (Method 2)
158	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)propan-1-one	1-Methyl-1H-imidazole-5-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.54 (s, 1H), 7.31 (dd, J=1.9, 11.9 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.16-7.13 (m, 1H), 7.13-7.08 (m, 1H), 6.73-6.72 (m, 1H), 6.16 (d, J=4.9 Hz, 1H), 3.94 (t, J=6.9 Hz, 1H), 3.60 (s, 3H), 3.53-3.34 (m, 6H), 2.79 (dd, J=6.4, 13.2 Hz, 1H), 2.68 (dd, J=7.3, 13.1 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.36-2.26 (m, 2H), 2.23-2.11 (m, 1H), 2.05-1.92 (m, 1H), 1.77 (s, 2H).	Rt = 3.08 min, m/z 492.2 [M+H] ⁺ (Method 2)
159	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(quinoxalin-2-ylmethyl)piperazin-1-yl)propan-1-one	Quinoxaline-2-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 9.03 (s, 1H), 8.12-8.05 (m, 2H), 8.02 (d, J=5.4 Hz, 1H), 7.87-7.82 (m, 2H), 7.32 (dd, J=1.9, 12.0 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 7.17-7.13 (m, 1H), 7.13-7.08 (m, 1H), 6.18 (d, J=5.0 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.84 (s, 2H), 3.58-3.37 (m, 4H), 2.81 (dd, J=6.4, 13.2 Hz, 1H), 2.68 (dd, J=7.3, 13.2 Hz, 1H), 2.48-2.43 (m, 2H), 2.40 (d, J=0.9 Hz, 3H), 2.37-2.28 (m, 1H), 2.25-2.13 (m, 1H), 1.79-1.74 (m, 2H).	Rt = 3.67 min, m/z 540.2 [M+H] ⁺ (Method 2)

Ex	Structure	Aldehyde	¹ H NMR	LC-MS
160	 (S)-2-amino-1-(4-(4-(3-(dimethylamino)propoxy)benzyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	4-(3-(Dimethylamino)propoxy)-benzaldehyde	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.30 (dd, J=1.9, 12.0 Hz, 1H), 7.24 (t, J=8.5 Hz, 1H), 7.17 (d, J=8.5 Hz, 2H), 7.15-7.13 (m, 1H), 7.12-7.07 (m, 1H), 6.86 (d, J=8.7 Hz, 2H), 6.16 (d, J=4.9 Hz, 1H), 3.98-3.92 (m, 3H), 3.55-3.30 (m, 6H), 2.79 (dd, J=6.5, 13.1 Hz, 1H), 2.67 (dd, J=7.3, 13.1 Hz, 1H), 2.39 (d, J=1.1 Hz, 3H), 2.36-2.27 (m, 4H), 2.18-2.14 (m, 1H), 2.13 (s, 6H), 2.01-1.92 (m, 1H), 1.87-1.77 (m, 2H), 1.72-1.72 (m, 2H).	Rt = 3.90 min, m/z 589.3 [M+H] ⁺ (Method 2)
161	 1-(Methanesulfonyl)piperidine-4-carbaldehyde	1-(Methanesulfonyl)piperidine-4-carbaldehyde	¹ H NMR (400 MHz, d6-DMSO) δ 11.41 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.30 (dd, J=1.9, 11.9 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.16-7.12 (m, 1H), 7.12-7.07 (m, 1H), 6.16 (d, J=5.4 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.59-3.48 (m, 3H), 3.45-3.32 (m, 3H), 2.83 (s, 3H), 2.78 (dd, J=7.2, 13.1 Hz, 1H), 2.74-2.61 (m, 3H), 2.38 (d, J=0.9 Hz, 3H), 2.37-2.28 (m, 2H), 2.13-2.04 (m, 3H), 1.97-1.85 (m, 1H), 1.81-1.68 (m, 4H), 1.67-1.53 (m, 1H), 1.17-1.04 (m, 2H).	Rt = 3.42 min, m/z 573.2 [M+H] ⁺ (Method 2)
162	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)propan-1-one	Pyrimidine-5-carbaldehyde	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 9.10 (s, 1H), 8.72 (s, 2H), 7.99 (d, J=5.4 Hz, 1H), 7.32 (dd, J=1.8, 11.9 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.17-7.13 (m, 1H), 7.13-7.08 (m, 1H), 6.16 (d, J=5.4 Hz, 1H), 3.93 (t, J=6.8 Hz, 1H), 3.52 (s, 2H), 3.50-3.36 (m, 4H), 2.80 (dd, J=6.2, 13.2 Hz, 1H), 2.67 (dd, J=7.5, 13.2 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.37-2.21 (m, 3H), 2.20-2.08 (m, 1H), 1.75-1.75 (m, 2H).	Rt = 3.06 min, m/z 490.1 [M+H] ⁺ (Method 2)

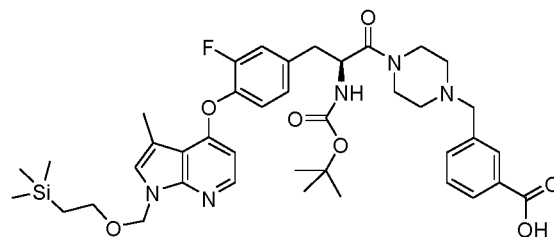
Ex	Structure	Aldehyde	¹ H NMR	LC-MS
163	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-pyrazol-4-yl)methyl)piperazin-1-yl)propan-1-one	1-Methyl-1H-pyrazole-4-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.53 (s, 1H), 7.33-7.21 (m, 3H), 7.13 (s, 1H), 7.10 (dd, J=1.3, 8.3 Hz, 1H), 6.15 (d, J=5.4 Hz, 1H), 3.92 (dd, J=6.8, 6.8 Hz, 1H), 3.78 (s, 3H), 3.49-3.34 (m, 4H), 3.29 (s, 2H), 2.78 (dd, J=6.3, 13.2 Hz, 1H), 2.66 (dd, J=7.3, 13.1 Hz, 1H), 2.38 (d, J=1.0 Hz, 3H), 2.34-2.26 (m, 2H), 2.17-2.11 (m, 1H), 2.08-2.02 (m, 1H), 1.79-1.64 (s, 2H).	Rt = 1.74 min, m/z 492.1 [M+H] ⁺ (Method 1)
164	 (S)-1-(4-((1,2,3-thiadiazol-4-yl)methyl)piperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1,2,3-Thiadiazole-4-carbaldehyde	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 9.05 (s, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.31 (dd, J=2.2, 12.2 Hz, 1H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.14-7.08 (m, 2H), 6.16 (d, J=5.4 Hz, 1H), 4.02 (s, 2H), 3.93 (dd, J=6.9, 6.9 Hz, 1H), 3.54-3.35 (m, 4H), 2.80 (dd, J=6.2, 13.2 Hz, 1H), 2.69-2.62 (m, 1H), 2.47-2.41 (m, 2H), 2.38 (d, J=1.0 Hz, 3H), 2.36-2.30 (m, 1H), 2.25-2.17 (m, 1H), 1.77 (s, 2H).	Rt = 2.09 min, m/z 496.0 [M+H] ⁺ (Method 1)

Example 165**Step A**

Methyl (S)-3-((4-(2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)benzoate (Intermediate 165A)

Intermediate 165A was prepared from Intermediate 152B and methyl 3-formylbenzoate using a method similar to that used for Step A of Example 153.

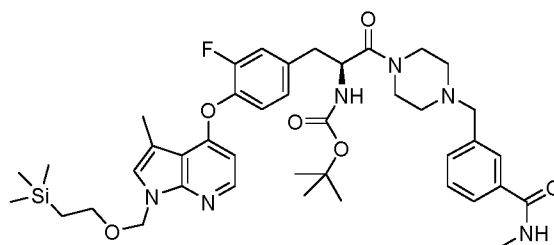
LCMS (Method 4): $R_t = 1.51$ min, m/z 776.4 $[M+H]^+$

Step B

(S)-3-((4-(2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)benzoic acid (Intermediate 165B)

Intermediate 165B was prepared from Intermediate 165A using a method similar to that used in Step E of Example 1.

LCMS (Method 4): $R_t = 1.42$ min, m/z 762.5 $[M+H]^+$

Step C

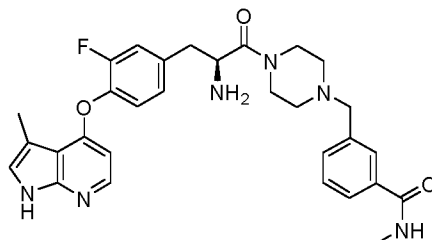
tert-Butyl (S)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)benzoate

1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(3-(methylcarbamoyl)benzyl)piperazin-1-yl)-1-oxopropan-2-yl)carbamate
(Intermediate 165C)

Intermediate 165C was prepared from Intermediate 165B and methylamine using a method similar to that used in Step F of Example 1.

LCMS (Method 4): $R_t = 1.37$ min, m/z 775.5 $[M+H]^+$

Step D



(S)-3-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)-N-methylbenzamide (Example 165)

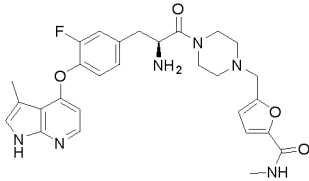
Example 165 was prepared from Intermediate 165C using a method similar to that used for in Step G of Example 1.

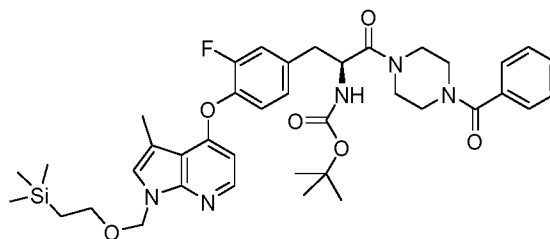
LCMS (Method 1): $R_t = 1.93$ min, m/z 545.2 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 11.41 (s, 1H), 8.42-8.38 (m, 1H), 7.98 (d, $J=5.4$ Hz, 1H), 7.75 (s, 1H), 7.73-7.69 (m, 1H), 7.41 (d, $J=6.5$ Hz, 2H), 7.31 (dd, $J=2.1, 12.0$ Hz, 1H), 7.24 (dd, $J=8.4, 8.4$ Hz, 1H), 7.14-7.08 (m, 2H), 6.16 (d, $J=5.4$ Hz, 1H), 3.93 (dd, $J=6.6, 6.6$ Hz, 1H), 3.49 (s, 3H), 3.46-3.41 (m, 3H), 2.84-2.76 (m, 4H), 2.67 (dd, $J=7.4, 13.1$ Hz, 1H), 2.38 (s, 3H), 2.37-2.30 (m, 2H), 2.23-2.18 (m, 1H), 2.06 (dd, $J=7.4, 7.4$ Hz, 1H), 1.70 (s, 2H).

Example 166

The following example was prepared using a similar method of Example 165 by replacing in Step A the aldehyde with that indicated in table below.

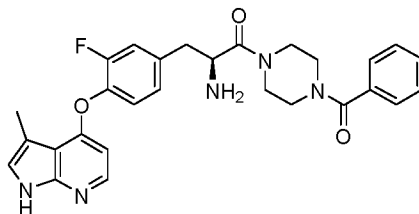
Ex	Structure	Aldehyde	¹ H NMR	LC-MS
166	 (S)-5-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propano-yl)piperazin-1-yl)methyl)-N-methylfuran-2-carboxamide	Methyl 5-formyl-furan-2-carboxylate	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.18 (q, J=4.5 Hz, 1H), 7.98 (d, J=5.4 Hz, 1H), 7.32 (dd, J=1.7, 11.8 Hz, 1H), 7.23 (dd, J=8.4, 8.4 Hz, 1H), 7.14-7.08 (m, 2H), 6.99 (d, J=3.3 Hz, 1H), 6.41 (d, J=3.4 Hz, 1H), 6.16 (d, J=5.4 Hz, 1H), 3.93 (dd, J=6.8, 6.8 Hz, 1H), 3.51 (s, 2H), 3.49-3.38 (m, 4H), 2.80 (dd, J=6.1, 13.3 Hz, 1H), 2.72 (d, J=4.6 Hz, 3H), 2.69-2.62 (m, 1H), 2.39-2.22 (m, 6H), 2.19-2.11 (m, 1H), 1.70 (s, 2H).	Rt = 1.95 min, m/z 535.2 [M+H] ⁺ (Method 1)

Example 167**Step A**

tert-Butyl (S)-1-(4-benzoylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl)carbamate (Intermediate 167A)

Intermediate 167A was prepared from Intermediate 152B and benzoic acid using conditions similar to those used in Step F of Example 1.

LCMS (Method 6): Rt = 1.81 min, m/z 732.3 [M+H]⁺

Step B

(S)-2-amino-1-(4-benzoylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (Example 167)

5 Example 167 was prepared from Intermediate 167A using a method similar to Step G of Example 1.

LCMS (Method 2): $R_t = 3.51$ min, m/z 502.0 $[M+H]^+$

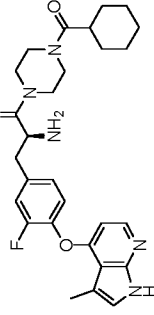
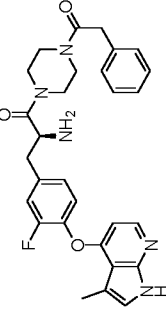
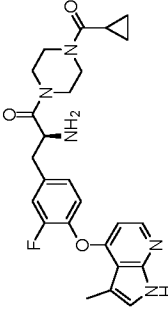
1H NMR (400 MHz, d_6 -DMSO) δ 11.40 (s, 1H), 7.96 (d, $J=5.4$ Hz, 1H), 7.47-7.38 (m, 5H), 7.35 (d, $J=11.8$ Hz, 1H), 7.24 (t, $J=8.4$ Hz, 1H), 7.14-7.10 (m, 2H), 6.13 (d, $J=5.4$ Hz, 1H), 3.94-3.94 (m, 1H), 3.71-3.37 (m, 7H), 3.26 – 3.01 (m, 1H), 2.84 (dd, $J=5.8, 13.2$ Hz, 1H), 2.72-2.65 (m, 1H), 2.38 (s, 3H), 1.75 (s, 2H).

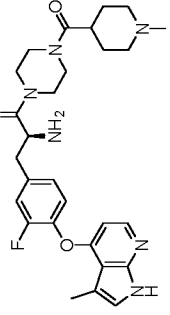
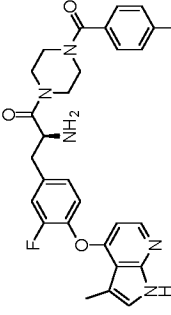
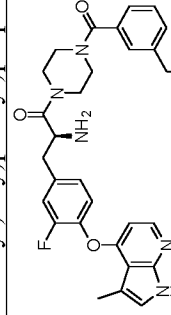
10

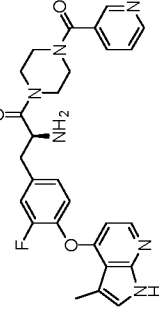
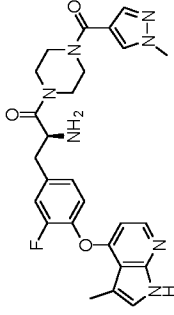
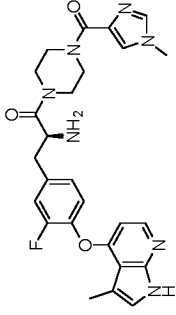
Example 168 to 177

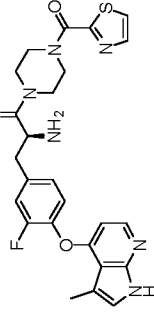
The following examples were prepared in a similar manner to Example 167 by replacing in Step A the corresponding carboxylic acid with those indicated in the table

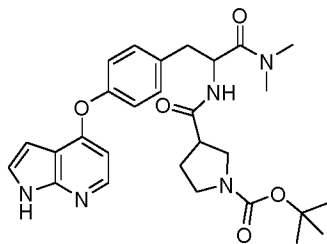
15 below.

Ex	Structure	Acid	¹ H NMR	LC-MS
168	 (S)-2-amino-1-(4-(cyclohexanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	Cyclohexane-carboxylic acid	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.95 (d, J=5.5 Hz, 1H), 7.34 (d, J=11.7 Hz, 1H), 7.28-7.20 (m, 1H), 7.15-7.10 (m, 2H), 6.13-6.08 (m, 1H), 3.97-3.92 (m, 1H), 3.54-3.38 (m, 6H), 3.21-3.13 (m, 1H), 2.82 (dd, J=6.2, 13.1 Hz, 1H), 2.70 (dd, J=7.2, 13.1 Hz, 1H), 2.61-2.53 (m, 1H), 2.37 (d, J=0.9 Hz, 3H), 1.80-1.61 (m, 7H), 1.30-1.15 (m, 6H).	Rt = 3.78 min, m/z 508.1 [M+H] ⁺ (Method 2)
169	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-phenylacetyl)piperazin-1-yl)propan-1-one	2-Phenylacetic acid	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.96 (d, J=5.4 Hz, 1H), 7.34-7.19 (m, 7H), 7.14-7.09 (m, 2H), 6.14-6.12 (m, 1H), 3.99-3.89 (m, 1H), 3.74 (s, 2H), 3.54-3.33 (m, 7H), 3.28-3.19 (m, 1H), 2.82 (dd, J=6.0, 13.4 Hz, 1H), 2.70-2.62 (m, 1H), 2.38 (s, 3H), 1.70 (s, 2H).	Rt = 3.62 min, m/z 516.1 [M+H] ⁺ (Method 2)
170	 (S)-2-amino-1-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	Cyclopropane-carboxylic acid	¹ H NMR (400 MHz, d6-DMSO) δ 11.40 (s, 1H), 7.95 (d, J=5.4 Hz, 1H), 7.34 (dd, J=1.6, 11.9 Hz, 1H), 7.24 (t, J=8.4 Hz, 1H), 7.15-7.10 (m, 2H), 6.11 (d, J=5.0 Hz, 1H), 3.97 (t, J=6.8 Hz, 1H), 3.74-3.36 (m, 7H), 3.28-3.12 (m, 1H), 2.83 (dd, J=6.3, 13.2 Hz, 1H), 2.70 (dd, J=7.4, 13.2 Hz, 1H), 2.38 (d, J=0.9 Hz, 3H), 2.01-1.92 (m, 1H), 1.76 (s, 2H), 0.74-0.69 (m, 4H).	Rt = 3.25 min, m/z 466.1 [M+H] ⁺ (Method 2)

Ex	Structure	Acid	¹ H NMR	LC-MS
171	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methylpiperidine-4-carbonyl)piperazin-1-yl)propan-1-one	1-Methyl-piperidine-4-carboxylic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.40 (s, 1H), 7.96 (d, J=5.4 Hz, 1H), 7.33 (d, J=11.7 Hz, 1H), 7.28-7.22 (m, 1H), 7.15-7.11 (m, 2H), 6.11 (s, 1H), 3.96-3.96 (m, 1H), 3.55-3.41 (m, 6H), 3.20-3.15 (m, 1H), 2.87-2.65 (m, 4H), 2.37 (d, J=0.8 Hz, 3H), 2.13 (s, 3H), 1.92-1.82 (m, 2H), 1.76 (s, 2H), 1.55-1.50 (m, 6H).	Rt = 1.84 min, m/z 523.1 [M+H] ⁺ (Method 1)
172	 (S)-2-amino-1-(4-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	4-((Dimethylamino)methyl)benzoic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.41 (d, J=1.7 Hz, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.40-7.37 (m, 5H), 7.27 (dd, J=8.4, 8.4 Hz, 1H), 7.15-7.11 (m, 2H), 6.15 (d, J=5.4 Hz, 1H), 4.13 (s, 2H), 3.56-3.42 (m, 1H), 2.91 (dd, J=5.7, 13.4 Hz, 1H), 2.78 (d, J=7.5 Hz, 1H), 2.38 (s, 3H), 2.16 (s, 6H).	Rt = 1.91 min, m/z 559.2 [M+H] ⁺ (Method 1)
173	 (S)-2-amino-1-(4-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	3-((Dimethylamino)methyl)benzoic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.44 (d, J=1.9 Hz, 1H), 7.98 (d, J=5.2 Hz, 1H), 7.56-7.46 (m, 3H), 7.46-7.38 (m, 2H), 7.32 (dd, J=8.3, 8.3 Hz, 1H), 7.17 (d, J=11.5 Hz, 2H), 6.20 (d, J=5.4 Hz, 1H), 4.67 (s, 1H), 3.90-3.47 (m, 1H), 3.18-3.01 (m, 3H), 2.46 (s, 6H), 2.38 (s, 3H).	Rt = 1.95 min, m/z 559.2 [M+H] ⁺ (Method 1)

Ex	Structure	Acid	¹ H NMR	LC-MS
174	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-nicotinoylpiperazin-1-yl)propan-1-one	Pyridine-3-carboxylic acid	¹ H NMR (400 MHz, DMSO) δ 11.40 (s, 1H), 8.67 (dd, J=1.7, 4.9 Hz, 1H), 8.63 (d, J=1.5 Hz, 1H), 7.97 (d, J=5.4 Hz, 1H), 7.87-7.82 (m, 1H), 7.49 (dd, J=4.9, 7.8 Hz, 1H), 7.35 (d, J=12.1 Hz, 1H), 7.24 (dd, J=8.3, 8.3 Hz, 1H), 7.16-7.10 (m, 2H), 6.14 (d, J=5.3 Hz, 1H), 3.97 (s, 2H), 3.59-3.50 (m, 7H), 2.87-2.81 (m, 1H), 2.73-2.66 (m, 1H), 2.38 (s, 3H).	Rt = 2.11 min, m/z 503.2 [M+H] ⁺ (Method 1)
175	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)propan-1-one	1-Methyl-1H-pyrazole-4-carboxylic acid	¹ H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 8.07 (s, 1H), 7.94 (d, J=5.4 Hz, 1H), 7.67 (s, 1H), 7.35 (dd, J=2.1, 12.1 Hz, 1H), 7.25 (dd, J=8.4, 8.4 Hz, 1H), 7.13 (dd, J=4.2, 4.2 Hz, 2H), 6.12 (d, J=5.4 Hz, 1H), 3.97 (dd, J=6.7, 6.7 Hz, 1H), 3.85 (s, 3H), 3.66-3.42 (m, 8H), 2.85 (dd, J=6.0, 13.3 Hz, 1H), 2.70 (dd, J=7.5, 13.2 Hz, 1H), 2.37 (s, 3H).	Rt = 2.17 min, m/z 506.3 [M+H] ⁺ (Method 3)
176	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-imidazole-4-carbonyl)piperazin-1-yl)propan-1-one	1-Methyl-1H-imidazole-4-carboxylic acid	¹ H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 7.66 (d, J=0.9 Hz, 2H), 7.36 (dd, J=1.9, 12.1 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.13 (dd, J=1.2, 6.4 Hz, 2H), 6.11 (d, J=5.2 Hz, 1H), 4.27-3.86 (m, 3H), 3.69 (s, 3H), 3.57-3.45 (m, 6H), 2.83 (dd, J=6.4, 13.2 Hz, 1H), 2.71 (dd, J=7.4, 13.2 Hz, 1H), 2.37 (s, 3H).	Rt = 2.06 min, m/z 506.3 [M+H] ⁺ (Method 3)

Ex	Structure	Acid	¹ H NMR	LC-MS
177	 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(thiazole-2-carbonyl)piperazin-1-yl)propan-1-one	Thiazole-2-carboxylic acid	¹ H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 8.07-8.02 (m, 2H), 7.91 (dd, J=4.8, 27.6 Hz, 1H), 7.36 (dd, J=1.7, 11.9 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.14 (d, J=9.2 Hz, 2H), 6.12 (d, J=5.1 Hz, 1H), 4.34-4.00 (m, 3H), 3.73-3.48 (m, 6H), 2.89-2.83 (m, 1H), 2.72-2.67 (m, 1H), 2.38-2.34 (m, 3H), 1.83-1.83 (m, 2H).	Rt = 2.45 min, m/z 509.3 [M+H] ⁺ (Method 3)

Example 178**Step A**

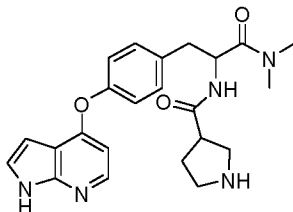
tert-Butyl 3-((3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-

5 **(dimethylamino)-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate**

(Intermediate 178A)

Example 113 (45 mg, 0.139 mmol), racemic 1-(tert-butoxycarbonyl)pyrrolidine-3-carboxylic acid (33 mg, 0.153 mmol) and DIPEA (72 μ L, 0.419 mmol) were dissolved in a mixture of DMF (2 mL) and DCM (5 mL). HATU (63 mg, 0.166 mmol) was added and
10 the reaction was stirred at RT overnight. Evaporation gave a residue which was used without further purification (82 mg).

LCMS (Method 6): R_t = 1.08 and 1.09 min, m/z 522.3 $[M+H]^+$

Step B

15 **N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(dimethylamino)-1-**
oxopropan-2-yl)pyrrolidine-3-carboxamide (Example 178)

Intermediate 178A (72 mg, crude) was dissolved in DCM (3 mL) and TFA (1 mL) was added. The reaction was stirred at RT overnight and then the volatiles were evaporated. The residue was dissolved in methanol and loaded on to 2 g SCX-2 cartridge which had
20 been conditioned with methanol. After flushing with methanol, the product was eluted with 2M ammonia in methanol. After evaporation of the solvent, the residue was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% formic acid added). The desired product was obtained as an off-white solid (24 mg).

LCMS (Method 3): Rt = 1.93 min, m/z 422.3 [M+H]⁺

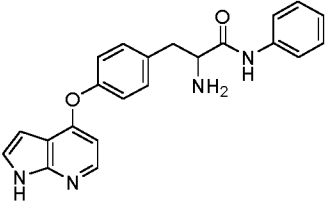
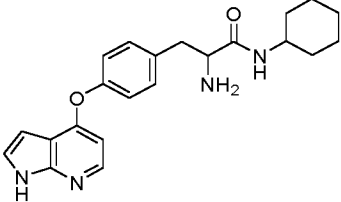
¹H NMR (400 MHz, d₆-DMSO) δ 11.72 (s, 1H), 8.45 (d, J=8.4 Hz, 1H), 8.33 (s, 1H), 8.07 (d, J=5.4 Hz, 1H), 7.33-7.30 (m, 3H), 7.10-7.07 (m, 2H), 6.36 (d, J=5.4 Hz, 1H), 6.14 (d, J=2.9 Hz, 1H), 4.96-4.88 (m, 1H), 3.07-2.96 (m, 2H), 2.95 (s, 3H), 2.93-2.88 (m, 2H), 2.87-2.77 (m, 2H), 2.82 (s, 3H), 2.74 (dd, J=6.5, 10.5 Hz, 1H), 1.97-1.73 (m, 2H).

Example 179 to 180

The following examples were prepared in a similar manner to Example 178 by replacing the appropriate starting material as indicated in the table below

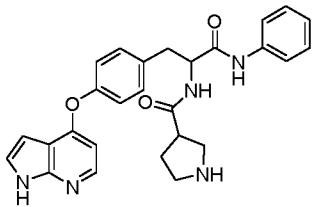
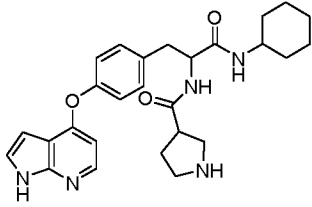
Preparation of Intermediates 179A to 180A

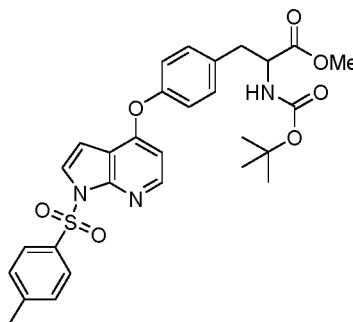
10 The following intermediates were prepared in a similar manner to Example 1 by replacing in Step 1 the intermediate 1E-a and amine with the corresponding starting materials indicated in the table below.

Intermediate	Structure	Starting materials	LC-MS
179A		1E-f and aniline	Rt = 2.28 min, m/z 373.0 [M+H] ⁺ (Method 3)
180A		1E-f and cyclohexanamine	Rt = 2.40 min, m/z 379.1 [M+H] ⁺ (Method 3)

Preparation of Examples

15 The following examples were prepared in a similar manner to Example 178 by replacing in Step A the starting material indicated in the table below.

Ex	Structure	Starting material	¹ H NMR	LC-MS
179	 N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-(phenylamino)propan-2-yl)pyrrolidine-3-carboxamide	Intermediate 179A	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.72 (s, 1H), 10.23-10.19 (m, 1H), 8.61-8.53 (m, 1H), 8.35 (s, 1H), 8.04 (d, J=5.4 Hz, 1H), 7.59 (d, J=7.6 Hz, 2H), 7.40-7.28 (m, 5H), 7.12-7.04 (m, 3H), 6.33-6.30 (m, 1H), 6.14-6.10 (m, 1H), 4.77-4.67 (m, 1H), 3.11-2.89 (m, 6H), 2.77 (dd, J=6.5, 10.9 Hz, 1H), 2.00-1.79 (m, 2H).	R _t = 2.38 min, m/z 470.3 [M+H] ⁺ (Method 3)
180	 N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)pyrrolidine-3-carboxamide	Intermediate 180A	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.73 (s, 1H), 8.39-8.30 (m, 2H), 8.06 (dd, J=1.3, 5.4 Hz, 1H), 7.96-7.89 (m, 1H), 7.36-7.32 (m, 1H), 7.30 (dd, J=2.3, 8.5 Hz, 2H), 7.08 (d, J=8.5 Hz, 2H), 6.35 (dd, J=5.5, 6.6 Hz, 1H), 6.17 (t, J=3.0 Hz, 1H), 4.59-4.48 (m, 1H), 3.18-2.91 (m, 6H), 2.84-2.73 (m, 1H), 2.00-1.79 (m, 1H), 1.73-1.50 (m, 6H), 1.27-1.05 (m, 6H).	R _t = 2.47/2.50 min, m/z 476.3 [M+H] ⁺ (Method 3)

Example 181**Step A**

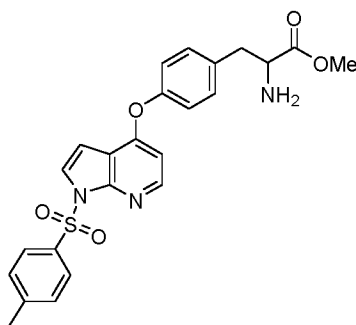
Methyl 2-((tert-butoxycarbonyl)amino)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate

b[pyridin-4-yl]oxy)phenyl]propanoate (Intermediate 181A)

Intermediate 181A was prepared from Intermediate 131A-a and methyl (tert-butoxycarbonyl)tyrosinate using a method similar to that used in Step D of Example 1.

LCMS (Method 6): $R_t = 1.69$ min, m/z 566.2 $[M+H]^+$

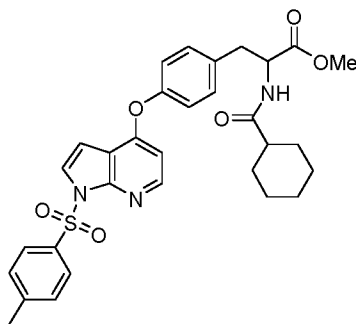
5

Step B**Methyl 2-amino-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 181B)**

Intermediate 181A (2.31 g, 4.09 mmol) was dissolved in DCM (10 mL) and TFA (2 mL) was added. The reaction was stirred at RT for 6 h and then the volatiles were evaporated. The residue was chromatographed on a 24 g Si cartridge eluting with 0-10% methanol in DCM to give the product as a beige solid (2.03 g)

10

LCMS (Method 6): $R_t = 1.07$ min, m/z 466.2 $[M+H]^+$

Step C

15

Methyl 2-(cyclohexanecarboxamido)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 181C)

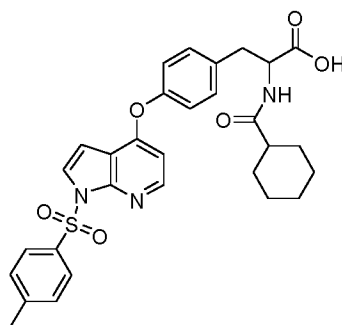
Intermediate 181B (250 mg, 0.538 mmol) was dissolved in DCM (10 mL) and DIPEA (140 μ L, 0.806 mmol) and cyclohexanecarbonyl chloride (87 μ L, 0.646 mmol) were added. The reaction was stirred at RT for 18 h and then diluted with DCM (20 mL).

20

The solution was washed with saturated ammonium chloride solution (10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated. The product was obtained as a solid (290 mg)

LCMS (Method 5): $R_t = 1.64$ min, m/z 576.3 $[\text{M}+\text{H}]^+$

5 **Step D**

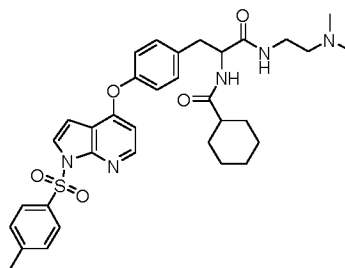


2-(Cyclohexanecarboxamido)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 181D)

Intermediate 181C (290 mg, 0.504 mmol) was dissolved in methanol (5 mL) and a solution of lithium hydroxide hydrate (32 mg, 0.762 mmol) in water (1 mL) was added. The reaction was stirred at RT overnight. The methanol was evaporated and the aqueous was adjusted to pH 5 by the addition of 1N HCl. The product was extracted into DCM (10 mL) and the solution was dried (Na_2SO_4) and evaporated to give the desired product as a solid (248 mg).

15 LCMS (Method 5): $R_t = 1.56$ min, m/z 562.2 $[\text{M}+\text{H}]^+$

Step E



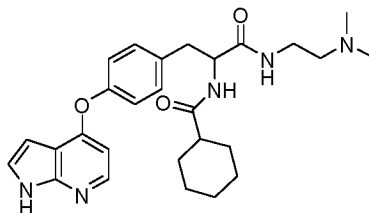
N-(1-((2-(Dimethylamino)ethyl)amino)-1-oxo-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-2-yl)cyclohexanecarboxamide (Intermediate 181E)

Intermediate 181E was prepared from Intermediate 181D and *N,N*-dimethylethane-

1,2-diamine using a similar method to that used in Step F of Example 1.

LCMS (Method 6): $R_t = 1.19$ min, m/z 632.4 $[M+H]^+$

Step F



5 **N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((2-(dimethylamino)ethyl)amino)-1-oxopropan-2-yl)cyclohexanecarboxamide (Example 181)**

Intermediate 181E (153 mg, 0.267 mmol) was dissolved in methanol (5 mL) and a solution of lithium hydroxide hydrate (22 mg, 0.533 mmol) in water (1.5 mL) was added.

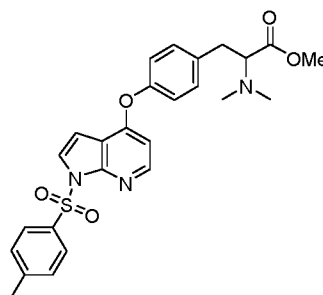
10 The reaction was stirred at RT for 1 h and then THF (3 mL) was added. Stirring was continued at 50°C for 2 h. The solvents were evaporated and the crude mixture was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH_4OH added). Example 181 was obtained as a white solid (30 mg).

LCMS (Method 1): $R_t = 2.49$ min, m/z 478.3 $[M+H]^+$

15 1H NMR (400 MHz, DMSO) δ 11.71 (s, 1H), 8.05-8.03 (m, 1H), 7.89 (d, $J=8.7$ Hz, 1H), 7.82 (dd, $J=5.4, 5.4$ Hz, 1H), 7.33-7.28 (m, 3H), 7.07 (d, $J=8.6$ Hz, 2H), 6.34 (d, $J=5.4$ Hz, 1H), 6.16 (d, $J=3.5$ Hz, 1H), 4.53-4.45 (m, 1H), 3.18-3.10 (m, 2H), 3.01 (dd, $J=4.7, 13.5$ Hz, 1H), 2.75 (dd, $J=10.1, 13.6$ Hz, 1H), 2.28-2.22 (m, 2H), 2.14-2.13 (m, 6H), 1.70-1.54 (m, 4H), 1.50-1.46 (m, 1H), 1.29-1.11 (m, 6H).

20 **Example 182**

Step A

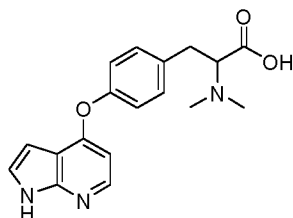


Methyl 2-(dimethylamino)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 182A)

Intermediate 181B (475 mg, 1.022 mmol) was dissolved in IMS (10 mL) and the solution was added to a flask containing 10% palladium on carbon (50 mg). Aqueous paraformaldehyde (37%, 0.61 mL, 8.18 mmol) was added and the vessel was evacuated and back-filled with hydrogen. The reaction was stirred at RT under an atmosphere of hydrogen for 18 h. The mixture was filtered through Celite® and the solvent was evaporated to give the desired product which was used without further purification (603 mg crude).

LCMS (Method 6): Rt = 1.13 min, m/z 494.2 [M+H]⁺

Step B

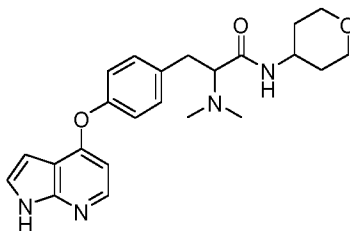


3-(4-((1H-Pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-(dimethylamino)propanoic acid (Intermediate 182B)

Intermediate 182A (504 mg, 1.02 mmol) was dissolved in methanol (10 mL) and a solution of lithium hydroxide hydrate (86 mg, 2.04 mmol) in water (2 mL) was added. The reaction was stirred at 50°C for 4 h and then at RT overnight. The solvents were evaporated *in vacuo* and the crude product was used in the next step without further purification.

LCMS (Method 6): Rt = 0.59 min, m/z 326.2 [M+H]⁺

Step C



3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-(dimethylamino)-N-(tetrahydro-2H-pyran-4-yl)propanamide (Example 182)

Example 182 was prepared from Intermediate 182B and tetrahydro-2H-pyran-4-

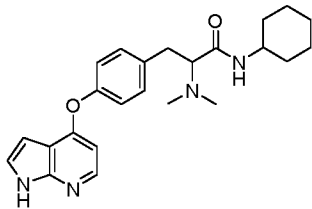
amine using a method similar to that used in Step F of Example 1.

LCMS (Method 1): $R_t = 1.95$ min, m/z 409.3 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 11.71 (s, 1H), 8.05 (d, $J=5.4$ Hz, 1H), 7.72 (d, $J=7.8$ Hz, 1H), 7.33 (d, $J=3.5$ Hz, 1H), 7.26 (d, $J=8.6$ Hz, 2H), 7.06 (d, $J=8.6$ Hz, 2H), 6.35 (d, $J=5.4$ Hz, 1H), 6.17 (d, $J=3.4$ Hz, 1H), 3.82-3.70 (m, 3H), 3.30-3.24 (m, 1H), 3.19-3.12 (m, 2H), 2.96 (dd, $J=9.6, 13.0$ Hz, 1H), 2.80 (dd, $J=5.0, 13.1$ Hz, 1H), 2.27 (s, 6H), 1.66-1.59 (m, 1H), 1.50-1.18 (m, 3H).

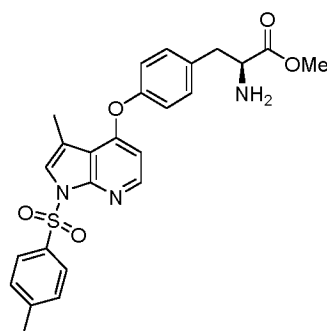
Example 183

The following example was prepared in a similar manner to Example 182 by replacing in Step C the amine indicated in the table below.

Ex	Structure	Starting materials	1H NMR	LC-MS
183	 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-(dimethylamino)propanamide	Cyclohexanamine	1H NMR (400 MHz, d_6 -DMSO) δ 11.70 (s, 1H), 8.04 (d, $J=5.4$ Hz, 1H), 7.56 (d, $J=8.1$ Hz, 1H), 7.32 (d, $J=3.4$ Hz, 1H), 7.25 (d, $J=8.6$ Hz, 2H), 7.06 (d, $J=8.5$ Hz, 2H), 6.34 (d, $J=5.4$ Hz, 1H), 6.18 (d, $J=3.4$ Hz, 1H), 3.55-3.46 (m, 1H), 3.16 (dd, $J=5.1, 9.6$ Hz, 1H), 2.96 (dd, $J=9.7, 13.0$ Hz, 1H), 2.77 (dd, $J=5.0, 13.0$ Hz, 1H), 2.26 (s, 6H), 1.69-1.47 (m, 5H), 1.27-0.94 (m, 5H).	$R_t = 2.48$ min, m/z 407.3 $[M+H]^+$ (Method 1)

Example 184

Step A

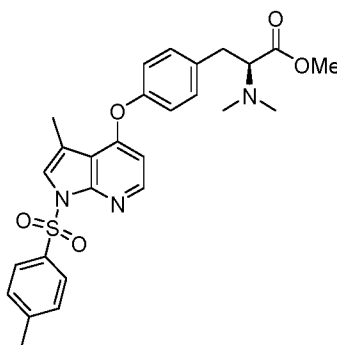


yl)oxy)phenyl)propanoate (Intermediate 184A)

Intermediate 184A was prepared from Intermediate 131E-c using a method similar to that used in Step G of Example 1.

LCMS (Method 8): $R_t = 1.18$ min, m/z 480.2 $[M+H]^+$

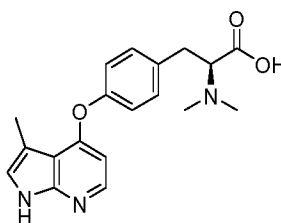
5

Step B**Methyl (S)-2-(dimethylamino)-3-(4-((3-methyl-1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 184B)**

Intermediate 184B was prepared from Intermediate 184A using a method similar to that used for Intermediate 182A.

10

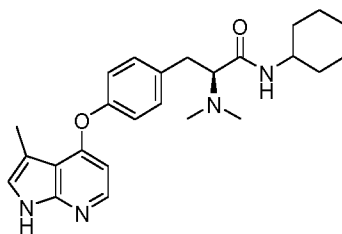
LCMS (Method 6): $R_t = 1.17$ min, m/z 508.4 $[M+H]^+$

Step C**(S)-2-(Dimethylamino)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-****yl)oxy)phenyl)propanoic acid (Intermediate 184C)**

Intermediate 184C was prepared from Intermediate 184B using a method similar to that used for Intermediate 182B.

LCMS (Method 6): $R_t = 0.71$ min, m/z 340.3 $[M+H]^+$

20

Step D

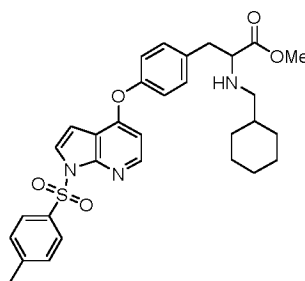
(S)-N-cyclohexyl-2-(dimethylamino)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (Example 184)

5 Example 184 was prepared from Intermediate 184C and cyclohexanamine using a method similar to that used for amide coupling in step F of Example 1.

LCMS (Method 1): $R_t = 2.59$ min, m/z 421.3 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 11.35 (s, 1H), 7.98-7.96 (m, 1H), 7.54 (d, $J=8.1$ Hz, 1H), 7.24 (d, $J=8.6$ Hz, 2H), 7.12 (s, 1H), 7.02 (d, $J=8.5$ Hz, 2H), 6.19 (d, $J=5.4$ Hz, 1H), 3.55-3.46 (m, 1H), 3.17-3.11 (m, 1H), 2.94 (dd, $J=9.6, 13.0$ Hz, 1H), 2.76 (dd, $J=5.1, 13.0$ Hz, 1H), 2.31 (d, $J=1.0$ Hz, 3H), 2.26 (s, 6H), 1.71-1.46 (m, 5H), 1.29-0.93 (m, 5H).

(ee% = 75%)

Example 185**Step A**

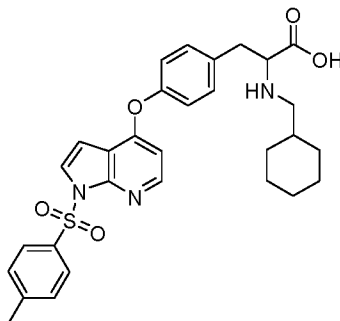
Methyl 2-((cyclohexylmethyl)amino)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 185A)

15 Intermediate 181B (250 mg, 0.538 mmol) and cyclohexanecarbaldehyde (72 μ L, 0.589 mmol) were dissolved in DCM (5 mL) and sodium triacetoxyborohydride (228 mg, 1.08 mmol) was added. The reaction was stirred at RT for 1 h. The reaction mixture was washed with saturated aqueous ammonium chloride (5 mL) and brine (5 mL), dried (Na_2SO_4) and evaporated. The product was used in the next reaction without purification

(255 mg).

LCMS (Method 5): $R_t = 1.26$ min, m/z 562.3 $[M+H]^+$

Step B

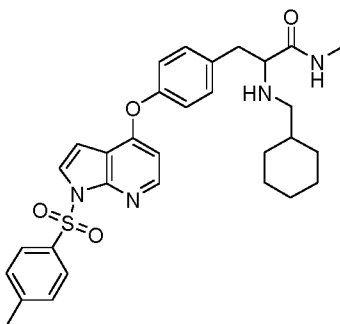


5 **2-((Cyclohexylmethyl)amino)-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 185B)**

Intermediate 185B was prepared from intermediate 185A using a procedure similar to that used in Step E of Example 1.

LCMS (Method 5): $R_t = 1.31$ min, m/z 548.2 $[M+H]^+$

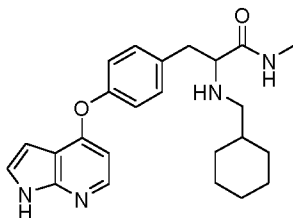
10 **Step C**



2-((Cyclohexylmethyl)amino)-N-methyl-3-(4-((1-tosyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (Intermediate 185C)

15 Intermediate 185C was prepared from intermediate 185B and methylamine (2M in THF) using a procedure similar to that used for step F of Example 1.

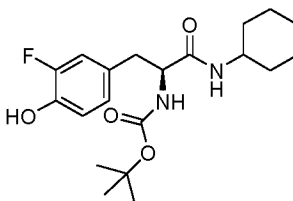
LCMS (Method 6): $R_t = 1.19$ min, m/z 561.3 $[M+H]^+$

Step D**3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-****((cyclohexylmethyl)amino)-N-methylpropanamide (Example 185)**

5 Example 185 was prepared from intermediate 185C using a procedure similar to that used for Step B of Example 182.

LCMS (Method 1): $R_t = 2.43$ min, m/z 407.3 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 11.71 (s, 1H), 8.06 (d, $J=5.4$ Hz, 1H), 7.77-7.70 (m, 1H), 7.32 (d, $J=3.5$ Hz, 1H), 7.27 (d, $J=8.4$ Hz, 2H), 7.08 (d, $J=8.5$ Hz, 2H), 6.37 (d, 10 $J=5.4$ Hz, 1H), 6.14 (d, $J=3.4$ Hz, 1H), 3.18-3.10 (m, 1H), 2.84 (dd, $J=6.0, 13.4$ Hz, 1H), 2.70 (dd, $J=7.9, 13.4$ Hz, 1H), 2.57 (d, $J=4.7$ Hz, 3H), 2.34-2.21 (m, 1H), 2.17-2.09 (m, 1H), 1.68-1.56 (m, 6H), 1.32-1.20 (m, 1H), 1.19-1.05 (m, 3H), 0.84-0.73 (m, 2H).

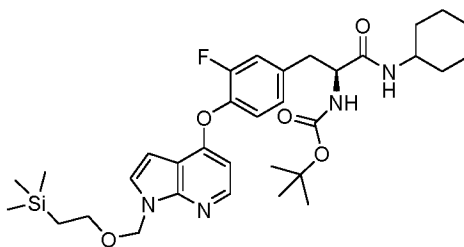
Example 186**Step A**

15

tert-Butyl (S)-1-(cyclohexylamino)-3-(3-fluoro-4-hydroxyphenyl)-1-oxopropan-2-ylcarbamate (Intermediate 186A)

Intermediate 186A was prepared from (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-hydroxyphenyl)propanoic acid and cyclohexanamine using a procedure similar to 20 that for Step F of Example 1.

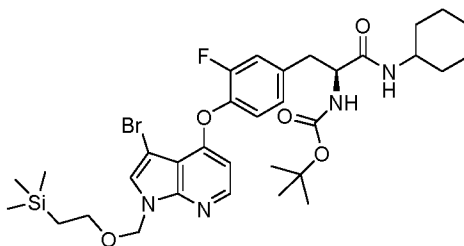
LCMS (Method 6): $R_t = 1.35$ min, m/z 403.3 $[M+Na]^+$

Step B

- tert-Butyl (S)-1-(cyclohexylamino)-3-(3-fluoro-4-((1-(2-(tert-butyl (trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl carbamate (Intermediate 186B)**

Intermediate 186B was prepared from Intermediate 186A and Intermediate 1C-c using a method similar to that used for Step D of Example 1.

LCMS (Method 6): $R_t = 1.84$ min, m/z 627.4 $[M+H]^+$

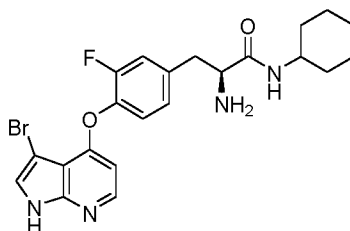
Step C

- tert-Butyl (S)-3-(4-((3-bromo-1-(2-(tert-butyl (trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl carbamate (Intermediate 186C)**

Intermediate 186B (580 mg, 0.927 mmol) was dissolved in acetonitrile (15 mL) and the solution was stirred at 0°C. NBS (173 mg, 0.972 mmol) was added and the reaction was stirred for 30 min at 0°C. Stirring was continued at RT for 1 h and then 1M sodium thiosulfate (15 mL) was added. The product was extracted into ethyl acetate (3 x 10 mL) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a 12 g Si cartridge eluting with 0-30% ethyl acetate in cyclohexane.

The pure product was obtained as a cream solid (351 mg).

LCMS (Method 6): $R_t = 1.91$ min, m/z 705.3/707.3 $[M+H]^+$

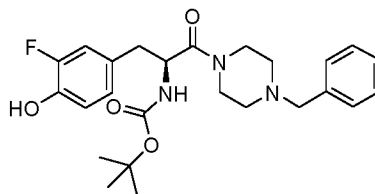
Step D

(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide (Example 186)

5 Example 186 was prepared from Intermediate 186C using a similar procedure to that used for Step G of Example 1.

LCMS (Method 1): $R_t = 3.08$ min, m/z 475.1/477.1 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 12.16 (s, 1H), 8.08 (d, $J=5.5$ Hz, 1H), 7.62 – 7.60 (m, 2H), 7.30-7.23 (m, 2H), 7.09 (d, $J=8.3$ Hz, 1H), 6.27-6.24 (m, 1H), 3.55-3.47 (m, 1H),
 10 3.40-3.35 (m, 1H), 2.88 (dd, $J=5.8, 13.2$ Hz, 1H), 2.71 (dd, $J=7.4, 13.2$ Hz, 1H), 1.82 (s, 2H), 1.69-1.49 (m, 5H), 1.32-1.02 (m, 5H).

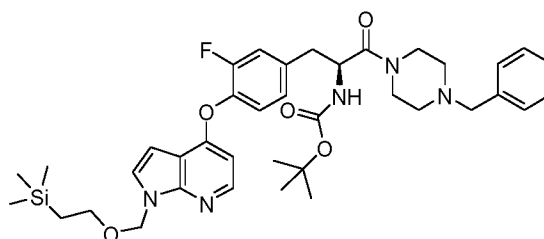
Example 187**Step A**

15 **tert-Butyl (S)-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-hydroxyphenyl)-1-oxopropan-2-yl carbamate (Intermediate 187A)**

Intermediate 187A was prepared from N-Boc-3-fluoro-L-tyrosine and 1-benzylpiperazine using a method similar to that used for Step F of Example 1.

LCMS (Method 6): $R_t = 0.94$ min, m/z 458.3 $[M+H]^+$

20 **Step B**

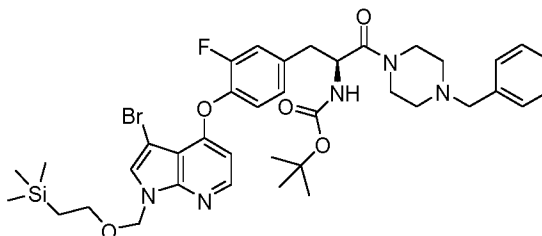


tert-Butyl (S)-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((1-(2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl)carbamate (Intermediate 187B)

Intermediate 187B was prepared from Intermediate 187A and Intermediate 1C-c using a similar procedure to that used for Step D of Example 1.

LCMS (Method 6): $R_t = 1.42$ min, m/z 704.4 $[M+H]^+$

Step C

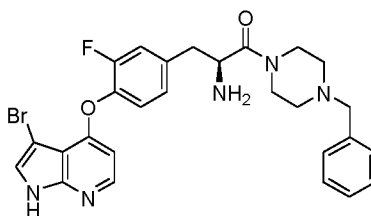


tert-Butyl (S)-1-(4-benzylpiperazin-1-yl)-3-(4-((3-bromo-1-(2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-1-oxopropan-2-yl)carbamate (Intermediate 187C)

Intermediate 187C was prepared from Intermediate 187B using a similar procedure to that used for Intermediate 186C.

LCMS (Method 6): $R_t = 1.49$ min, m/z 782.3/784.3 $[M+H]^+$

Step D



(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)propan-1-one (Example 187)

Example 187 was synthesized from Intermediate 187C using a similar procedure to that used for Step G of Example 1.

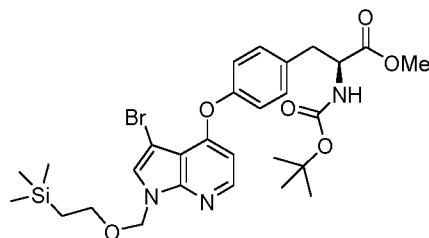
LCMS (Method 1): $R_t = 2.42$ min, m/z 552.2 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 12.17 (s, 1H), 8.09 (d, $J=5.4$ Hz, 1H), 7.63 (s, 1H), 7.35-7.24 (m, 6H), 7.12 (d, $J=8.3$ Hz, 1H), 6.27-6.25 (m, 1H), 3.94 (t, $J=6.9$ Hz, 1H), 3.55-

3.38 (m, 5H), 2.80 (dd, $J=6.4, 13.1$ Hz, 1H), 2.68 (dd, $J=7.3, 13.3$ Hz, 1H), 2.34-2.33 (m, 2H), 2.20-2.16 (m, 1H), 2.04 (m, 1H), 1.78-1.78 (m, 2H).

Example 188

Step A

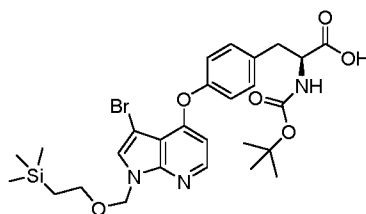


Methyl (S)-3-(4-((3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (Intermediate 188A)

Intermediate 188A was prepared from Intermediate 1D-e using a procedure similar to that of Intermediate 186C.

LCMS (Method 6): $R_t = 1.88$ min, m/z 620.2/622.2 $[M+H]^+$

Step B

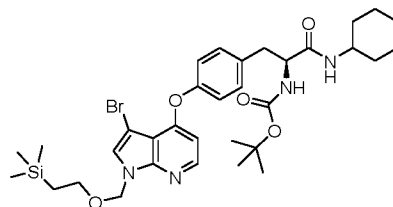


(S)-3-(4-((3-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-((tert-butoxycarbonyl)amino)propanoic acid (Intermediate 188B)

Intermediate 188B was prepared from Intermediate 188A using a procedure similar to that in Step E of Example 1.

LCMS (Method 6): $R_t = 1.79$ min, m/z 606.2/608.2 $[M+H]^+$

Step C

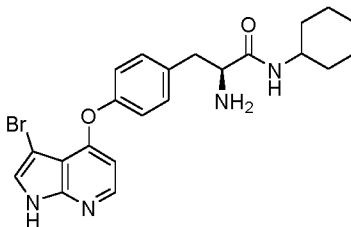


tert-Butyl (S)-3-(4-((3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)carbamate (Intermediate 188C)

Intermediate 188C was prepared from Intermediate 188B and cyclohexanamine using a procedure similar to that used for Step F of Example 1.

LCMS (Method 6): $R_t = 1.91$ min, m/z 687.3/689.3 $[M+H]^+$

Step D



(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide (Example 188)

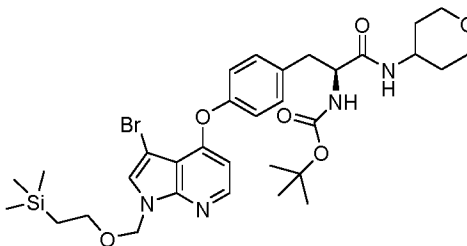
Example 188 was prepared from Intermediate 188C using a similar procedure to that used for Step G of Example 1.

LCMS (Method 1): $R_t = 3.01$ min, m/z 457.1/459.1 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 12.11 (s, 1H), 8.07 (d, $J=5.4$ Hz, 1H), 7.60-7.58 (m, 2H), 7.28 (d, $J=8.6$ Hz, 2H), 7.10-7.07 (m, 2H), 6.29 (d, $J=5.4$ Hz, 1H), 3.55-3.46 (m, 1H), 3.39-3.35 (m, 1H), 2.87 (dd, $J=5.8, 13.2$ Hz, 1H), 2.68 (dd, $J=7.4, 13.3$ Hz, 1H), 1.76-1.75 (m, 2H), 1.69-1.54 (m, 4H), 1.29-1.16 (m, 3H), 1.16-1.02 (m, 3H).

Example 189

Step A



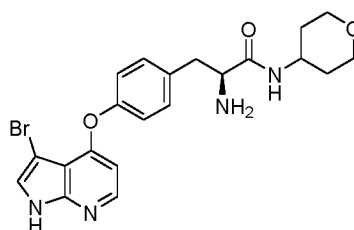
tert-Butyl (S)-3-(4-((3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-((tetrahydro-2H-pyran-4-

yl)amino)propan-2-yl)carbamate (Intermediate 189A)

Intermediate 189A was prepared from Intermediate 188B and tetrahydro-2H-pyran-4-amine using a procedure similar to that used for Step F of Example 1.

LCMS (Method 8): $R_t = 1.76$ min, m/z 689.3/691.3 $[M+H]^+$

5

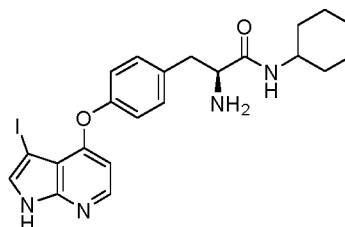
Step B**(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide (Example 189)**

Example 189 was prepared from Intermediate 189A using a similar procedure to that used for deprotection of step G of Example 1.

LCMS (Method 1): $R_t = 2.49$ min, m/z 459.1/461.1

1H NMR (400 MHz, d_6 -DMSO) δ 12.12 (s, 1H), 8.08 (d, $J=5.4$ Hz, 1H), 7.73-7.69 (m, 1H), 7.59 (s, 1H), 7.28 (d, $J=8.6$ Hz, 2H), 7.09 (d, $J=8.5$ Hz, 2H), 6.30 (d, $J=5.4$ Hz, 1H), 3.83-3.70 (m, 3H), 3.40-3.34 (m, 3H), 2.87 (dd, $J=5.9, 13.2$ Hz, 1H), 2.69 (dd, $J=7.4, 13.2$ Hz, 1H), 1.82 (s, 2H), 1.66-1.55 (m, 2H), 1.43-1.26 (m, 2H).

15

Example 190**(S)-2-amino-N-cyclohexyl-3-(4-((3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (Example 190)**

Example 190 was prepared similarly to Example 186 by substituting NBS with NIS in Step C.

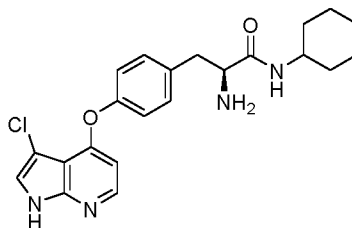
LCMS (Method 1): $R_t = 3.03$ min, m/z 505.1 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 12.13 (s, 1H), 8.06 (d, $J=5.4$ Hz, 1H), 7.60 (s,

20

1H), 7.58 (d, J=8.3 Hz, 1H), 7.28 (d, J=8.5 Hz, 2H), 7.07 (d, J=8.5 Hz, 2H), 6.29 (d, J=5.4 Hz, 1H), 3.55-3.46 (m, 1H), 3.39-3.34 (m, 1H), 2.87 (dd, J=5.8, 13.2 Hz, 1H), 2.67 (dd, J=7.5, 13.2 Hz, 1H), 1.72-1.52 (m, 6H), 1.30-1.02 (m, 6H).

Example 191



(S)-2-amino-3-(4-((3-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide (Example 191)

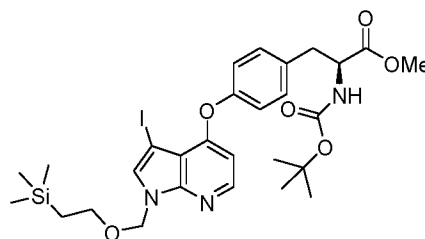
Example 191 was prepared similarly to Example 186 by substituting in Step C NBS with NCS.

LCMS (Method 1): Rt = 2.96 min, m/z 413.2 [M+H]⁺

¹H NMR (400 MHz, d₆-DMSO) δ 12.03 (s, 1H), 8.08 (d, J=5.4 Hz, 1H), 7.60-7.55 (m, 2H), 7.28 (d, J=8.6 Hz, 2H), 7.09 (d, J=8.6 Hz, 2H), 6.29 (d, J=5.5 Hz, 1H), 3.55-3.46 (m, 1H), 3.39-3.34 (m, 1H), 2.87 (dd, J=5.8, 13.2 Hz, 1H), 2.68 (dd, J=7.4, 13.3 Hz, 1H), 1.76 (s, 1H), 1.70-1.52 (m, 5H), 1.29-1.05 (m, 6H).

Example 192

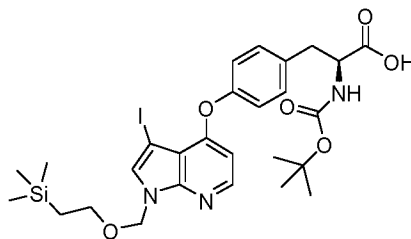
Step A



Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 192A)

Intermediate 192A was prepared from Intermediate 1D-e in a similar manner to Intermediate 186C using NIS rather than NBS.

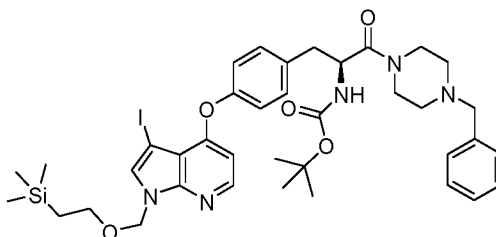
LCMS (Method 4): Rt = 1.91 min, m/z 668.0 [M+H]⁺

Step B

(S)-2-(((tert-Butoxycarbonyl)amino)-3-(4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 192B)

Intermediate 192B was prepared from Intermediate 192A in a similar manner to Step E of Example 1.

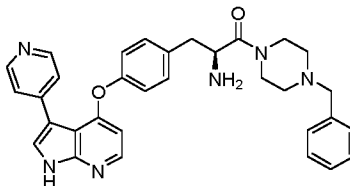
LCMS (Method 4): $R_t = 1.83$ min, m/z 654.0 $[M+H]^+$

Step C

tert-Butyl (S)-1-(4-benzylpiperazin-1-yl)-3-(4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl)carbamate (Intermediate 192C)

Intermediate 192C was prepared from Intermediate 192B and 1-benzylpiperazine using the same conditions to those used for Step F of Example 1.

LCMS (Method 4): $R_t = 2.64$ min, m/z 812.1 $[M+H]^+$

Step D

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (Example 192)

Intermediate 192C (200 mg, 0.247 mmol), pyridine-4-boronic acid (61 mg, 0.496

mmol), PdCl₂(dppf)₂.CH₂Cl₂ (10 mg, 0.012 mmol), and potassium carbonate (75 mg, 0.543 mmol) in a mixture of DME (3 mL) and water (1 mL) was bubbled with argon for 5 min. The mixture was stirred at 90°C for 18 h and then allowed to cool to RT. The mixture was applied to a 5 g SCX-2 cartridge which was then flushed with DCM and methanol. The product was eluted with 2M ammonia in methanol and evaporation gave a residue which was taken up into DCM (5 mL). TFA (2 mL) was added and the solution was stirred at RT overnight. After removal of the volatile components *in vacuo*, the product was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH₄OH added). The desired compound was obtained as a white solid (53 mg).

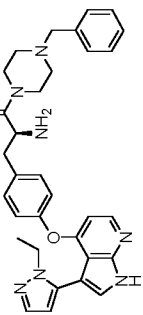
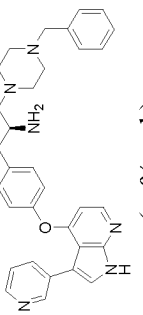
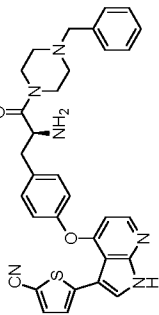
10 LCMS (Method 1): Rt = 1.69 min, m/z 533.1 [M+H]⁺

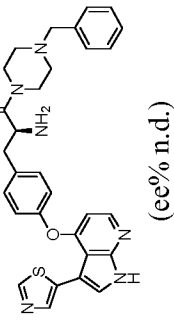
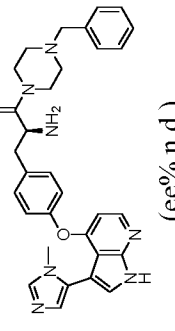
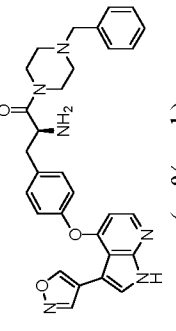
¹H NMR (400 MHz, d₆-DMSO) δ 12.25 (s, 1H), 8.47-8.45 (m, 2H), 8.11 (d, J=5.5 Hz, 1H), 7.92 (s, 1H), 7.74-7.71 (m, 2H), 7.32-7.24 (m, 6H), 7.14 (d, J=8.5 Hz, 2H), 6.34 (d, J=5.4 Hz, 1H), 3.91 (dd, J=6.9, 6.9 Hz, 1H), 3.57 (s, 3H), 3.43-3.38 (m, 5H), 2.77 (dd, J=6.7, 13.1 Hz, 1H), 2.70-2.62 (m, 1H), 2.35-2.17 (m, 3H), 2.06-2.02 (m, 1H), 1.71 (s, 1H).

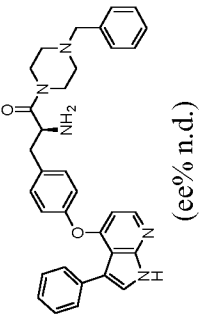
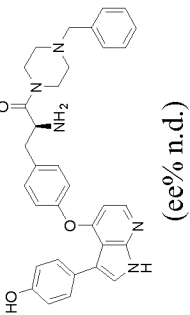
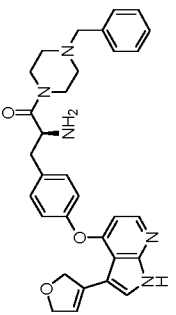
15 (ee% n.d.)

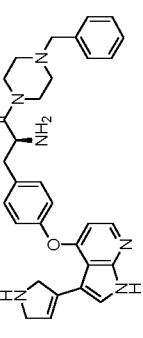
Example 193 to 202

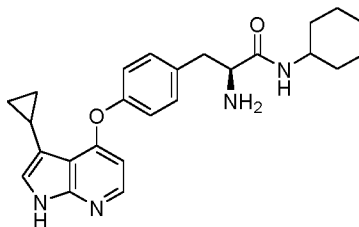
The following examples were prepared in a similar manner as Example 192, by replacing in Step D the boronic acid or boronate ester indicated the table below.

Ex	Structure	Boronic acid	¹ H NMR	LC-MS
193	 (ee% n.d.) (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-ethyl-1H-pyrazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	1-Ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.16 (s, 1H), 8.09 (d, J=5.4 Hz, 1H), 7.55 (s, 1H), 7.37 (d, J=1.8 Hz, 1H), 7.34-7.21 (m, 6H), 6.99 (d, J=8.6 Hz, 2H), 6.28-6.24 (m, 2H), 4.09 (q, J=7.2 Hz, 2H), 3.88 (dd, J=6.8, 6.8 Hz, 1H), 3.57 (s, 2H), 3.45-3.39 (m, 5H), 2.75 (dd, J=6.6, 13.1 Hz, 1H), 2.67-2.60 (m, 1H), 2.34-2.28 (m, 2H), 2.23-2.18 (m, 1H), 2.06-2.02 (m, 1H), 1.69 (s, 2H), 1.25 (dd, J=7.2, 7.2 Hz, 3H).	Rt = 2.16 min, m/z 550.1 [M+H] ⁺ (Method 1)
194	 (ee% n.d.) (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one	3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.17 (s, 1H), 8.88 (d, J=1.6 Hz, 1H), 8.36 (dd, J=1.6, 4.7 Hz, 1H), 8.11-8.03 (m, 2H), 7.74 (s, 1H), 7.36-7.24 (m, 8H), 7.11 (d, J=8.6 Hz, 2H), 6.31 (d, J=5.4 Hz, 1H), 3.90 (dd, J=6.8, 6.8 Hz, 1H), 3.57 (s, 1H), 3.47-3.39 (m, 5H), 2.77 (dd, J=6.6, 13.1 Hz, 1H), 2.65 (dd, J=7.1, 13.1 Hz, 1H), 2.33-2.26 (m, 2H), 2.22-2.18 (m, 1H), 2.06-2.02 (m, 1H), 1.71 (s, 2H).	Rt = 1.86 min, m/z 533.1 [M+H] ⁺ (Method 1)
195	 (ee% n.d.) (S)-5-(4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)phenoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carbonitrile	(5-Cyanothiophen-2-yl)boronic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.38 (s, 1H), 8.11 (d, J=5.4 Hz, 1H), 8.04 (s, 1H), 7.83 (d, J=4.0 Hz, 1H), 7.53 (d, J=3.9 Hz, 1H), 7.34-7.28 (m, 4H), 7.25 (d, J=7.1 Hz, 3H), 7.18 (d, J=8.6 Hz, 2H), 6.36 (d, J=5.4 Hz, 1H), 3.92 (dd, J=6.8, 6.8 Hz, 1H), 3.48-3.39 (m, 5H), 2.79 (dd, J=6.7, 13.1 Hz, 1H), 2.71-2.64 (m, 1H), 2.53 (d, J=6.8 Hz, 1H), 2.35-2.30 (m, 2H), 2.18-2.16 (m, 1H), 2.05-2.02 (m, 1H), 1.74 (s, 2H).	Rt = 2.53 min, m/z 563.1 [M+H] ⁺ (Method 1)

Ex	Structure	Boronic acid	¹ H NMR	LC-MS
196	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.22 (s, 1H), 8.88 (d, J=0.7 Hz, 1H), 8.12-8.09 (m, 2H), 7.82 (s, 1H), 7.32-7.24 (m, 6H), 7.14 (d, J=8.6 Hz, 2H), 6.33 (d, J=5.4 Hz, 1H), 3.91 (dd, J=6.8, 6.8 Hz, 1H), 3.48-3.38 (m, 7H), 2.78 (dd, J=6.7, 13.1 Hz, 1H), 2.70-2.63 (m, 1H), 2.36-2.27 (m, 2H), 2.21-2.16 (m, 1H), 2.03 (dd, J=7.7, 7.7 Hz, 1H), 1.70-1.70 (m, 2H).	Rt = 2.12 min, m/z 539.1 [M+H] ⁺ (Method 1)
197	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-methyl-1H-imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	1-Methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-imidazole	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.08 (s, 1H), 8.08 (d, J=5.4 Hz, 1H), 7.57 (s, 1H), 7.51 (d, J=1.9 Hz, 1H), 7.34-7.23 (m, 6H), 7.01 (d, J=8.6 Hz, 2H), 6.89 (d, J=1.1 Hz, 1H), 6.27 (d, J=5.5 Hz, 1H), 3.91 (dd, J=6.8, 6.8 Hz, 1H), 3.57 (s, 3H), 3.49-3.38 (m, 5H), 2.77 (dd, J=6.4, 13.2 Hz, 1H), 2.68-2.60 (m, 1H), 2.34-2.20 (m, 4H), 2.12-2.05 (m, 2H).	Rt = 1.59 min, m/z 536.2 [M+H] ⁺ (Method 1)
198	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(isoxazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.09-12.05 (m, 1H), 9.00 (d, J=16.1 Hz, 2H), 8.08 (d, J=5.5 Hz, 1H), 7.83 (s, 1H), 7.33-7.24 (m, 7H), 7.19 (d, J=8.6 Hz, 2H), 6.30 (d, J=5.4 Hz, 1H), 3.92 (dd, J=6.9, 6.9 Hz, 1H), 3.46-3.36 (m, 6H), 2.82-2.64 (m, 2H), 2.34-2.27 (m, 2H), 2.15 (dd, J=7.7, 7.7 Hz, 1H), 1.98 (dd, J=7.7, 7.7 Hz, 1H).	Rt = 2.14 min, m/z 523.1 [M+H] ⁺ (Method 1)

Ex	Structure	Boronic acid	¹ H NMR	LC-MS
199	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	Phenylboronic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 12.00 (s, 1H), 8.07 (d, J=5.4 Hz, 1H), 7.69-7.66 (m, 2H), 7.59 (s, 1H), 7.34-7.24 (m, 9H), 7.20-7.14 (m, 1H), 7.08 (d, J=8.6 Hz, 2H), 6.29 (d, J=5.4 Hz, 1H), 3.90 (t, J=6.9 Hz, 1H), 3.47-3.39 (m, 5H), 3.27-3.23 (m, 1H), 2.76 (dd, J=6.7, 13.1 Hz, 1H), 2.65 (dd, J=7.0, 13.1 Hz, 1H), 2.34-2.18 (m, 3H), 2.10-2.03 (m, 1H), 1.71 (s, 2H).	Rt = 2.50 min, m/z 532.2 [M+H] ⁺ (Method 1)
200	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	(4-((tert-Butyldimethylsilyl)oxy)phenyl)boronic acid	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.83 (s, 1H), 9.25 (s, 1H), 8.04 (d, J=5.4 Hz, 1H), 7.46-7.42 (m, 3H), 7.33-7.23 (m, 6H), 7.06 (d, J=8.6 Hz, 2H), 6.72-6.69 (m, 2H), 6.26 (d, J=5.4 Hz, 1H), 3.89 (dd, J=6.9, 6.9 Hz, 1H), 3.57 (s, 1H), 3.48-3.39 (m, 6H), 2.76 (dd, J=6.7, 13.1 Hz, 1H), 2.68-2.60 (m, 1H), 2.35-2.27 (m, 2H), 2.21 (d, J=5.5 Hz, 1H), 2.09-2.04 (m, 1H), 1.68-1.68 (m, 2H).	Rt = 2.06 min, m/z 548.2 [M+H] ⁺ (Method 1)
201	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydrofuran-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (ee% n.d.)	2-(2,5-Dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane	¹ H NMR (400 MHz, DMSO) δ 11.97 (s, 1H), 8.06 (d, J=5.5 Hz, 1H), 7.45 (s, 1H), 7.33-7.24 (m, 7H), 7.14 (d, J=8.6 Hz, 2H), 6.42-6.39 (m, 1H), 6.30 (d, J=5.4 Hz, 1H), 4.90-4.85 (m, 2H), 4.66-4.61 (m, 2H), 3.92 (dd, J=6.8, 6.8 Hz, 1H), 3.46-3.36 (m, 6H), 2.82-2.64 (m, 2H), 2.34-2.30 (m, 2H), 2.16 (dd, J=7.7, 7.7 Hz, 1H), 1.97 (dd, J=7.9, 7.9 Hz, 1H), 1.72-1.72 (m, 2H).	Rt = 2.12 min, m/z 524.2 [M+H] ⁺ (Method 1)

Ex	Structure	Boronic acid	¹ H NMR	LC-MS
202	 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydro-1H-pyridin-4-yl)oxy)phenyl)propan-1-one	tert-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate	¹ H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 8.04 (dd, J=4.6, 4.6 Hz, 1H), 7.55-7.37 (m, 1H), 7.34-7.24 (m, 7H), 7.12 (dd, J=7.6, 7.6 Hz, 2H), 6.37 (s, 1H), 6.28 (d, J=5.4 Hz, 1H), 4.29 (d, J=121.7 Hz, 1H), 3.97-3.89 (m, 2H), 3.69 (s, 1H), 3.47-3.37 (m, 8H), 2.81-2.64 (m, 2H), 2.36-2.30 (m, 2H), 2.19-2.17 (m, 1H), 2.02 (s, 1H).	Rt = 1.59 min, m/z 523.2 [M+H] ⁺ (Method 1)

Example 203

(S)-2-amino-N-cyclohexyl-3-(4-((3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (Example 203)

5 Example 203 was prepared from Intermediate 188C and cyclopropylboronic acid using a method similar to step D of Example 192.

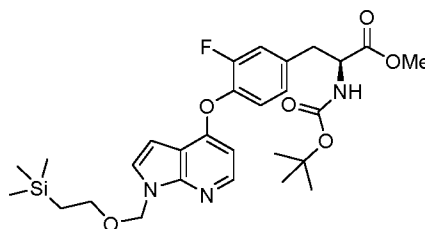
LCMS (Method 1): $R_t = 2.75$ min, m/z 419.3 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 11.37 (s, 1H), 7.99 (d, $J=5.4$ Hz, 1H), 7.57 (d, $J=8.1$ Hz, 1H), 7.25 (d, $J=8.6$ Hz, 2H), 7.05 (d, $J=8.6$ Hz, 2H), 7.02 (d, $J=2.0$ Hz, 1H), 6.26 (d, $J=5.4$ Hz, 1H), 3.54-3.45 (m, 1H), 3.38-3.34 (m, 1H), 2.85 (dd, $J=5.9, 13.2$ Hz, 1H), 2.67 (dd, $J=7.5, 13.1$ Hz, 1H), 2.08-2.02 (m, 1H), 1.72-1.61 (m, 5H), 1.55-1.51 (m, 1H), 1.28-1.01 (m, 6H), 0.77-0.71 (m, 2H), 0.60-0.55 (m, 2H).

ee% = 82%

Example 204

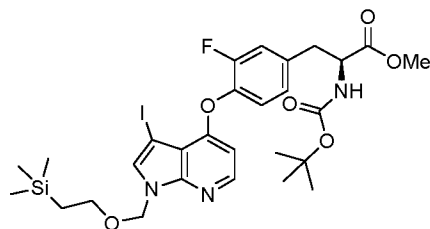
15 **Step A**



Methyl (S)-2-(((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 204A)

20 Intermediate 204A was prepared from Intermediate 1C-c and Intermediate 1A-a using a method similar to that of Step D of Example 1.

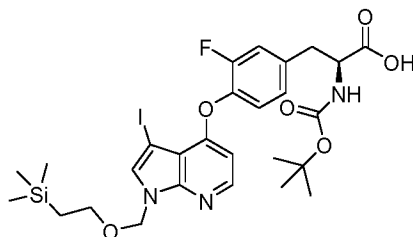
LCMS (Method 6): $R_t = 1.99$ min, m/z 560.3 $[M+H]^+$

Step B

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-propanoate (Intermediate 204B)

Intermediate 204B was prepared from Intermediate 204A using a procedure similar to that used for Intermediate 186C substituting NBS with NIS.

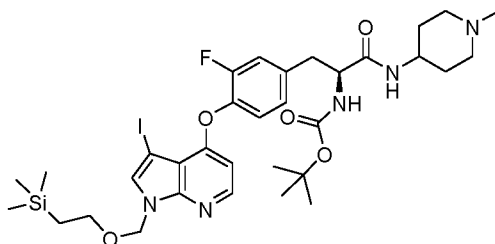
LCMS (Method 4): $R_t = 2.09$ min, m/z 686.3 $[M+H]^+$

Step C

(S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 204C)

Intermediate 204C was prepared from Intermediate 204B using the same method as that used in Step E of Example 1.

LCMS (Method 9): $R_t = 2.70$ min, m/z 672.1 $[M+H]^+$

Step D

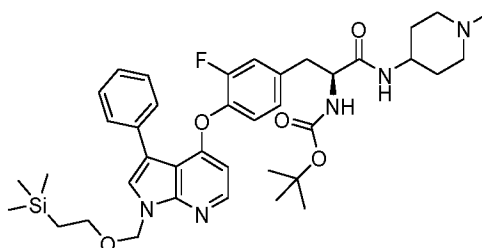
tert-butyl (S)-3-(3-fluoro-4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1-methylpiperidin-4-yl)amino)-1-

oxopropan-2-yl)carbamate (Intermediate 204D)

Intermediate 204D was prepared from Intermediate 204C and 1-methylpiperidin-4-amine using a procedure similar to that used in Step F of Example 1.

LCMS (Method 4): $R_t = 1.51$ min, m/z 768.3 $[M+H]^+$

5

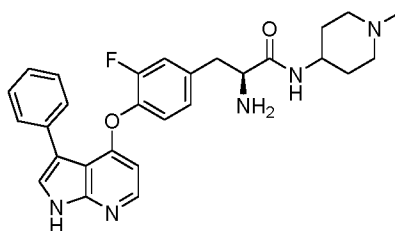
Step E

tert-Butyl (S)-(3-(3-fluoro-4-((3-phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1-methylpiperidin-4-yl)amino)-1-oxopropan-2-yl)carbamate (Intermediate 204E)

10 A mixture of Intermediate 204D (500 mg, 0.651 mmol), 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (266 mg, 1.30 mmol), $Pd_2Cl_2(dppf).CH_2Cl_2$ (27 mg, 0.033 mmol), potassium carbonate (198 mg, 1.43 mmol), DME (4 mL) and water (0.4 mL) was heated at 95°C for 19 h. After cooling, the mixture was filtered through Celite®. The solution was diluted with ethyl acetate (20 mL), washed with water (10 mL) and dried

15 (Na_2SO_4) . Evaporation gave a crude product which was chromatographed on a Si cartridge (24 g) eluting with 0-100% ethyl acetate in cyclohexane then 0-10% methanol in DCM. Pure product was obtained a colourless foam (180 mg).

LCMS (Method 4): $R_t = 1.35$ min, m/z 718.5 $[M+H]^+$

Step F

20

(S)-2-amino-3-(3-fluoro-4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide (Example 204)

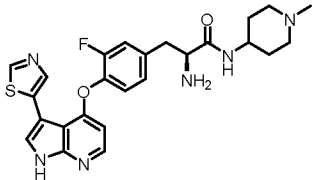
Example 204 was prepared from Intermediate 204E using a method similar to that used for Step G of Example 1.

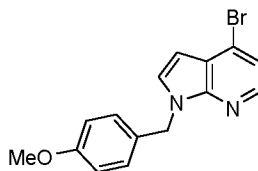
5 LCMS (Method 1): Rt = 2.21 min, m/z 488.2 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 12.04 (s, 1H), 8.07 (d, J=5.4 Hz, 1H), 7.70-7.60 (m, 4H), 7.36-7.18 (m, 5H), 7.07 (dd, J=1.3, 8.4 Hz, 1H), 6.24 (d, J=5.2 Hz, 1H), 3.51-3.43 (m, 1H), 3.37 (t, J=6.7 Hz, 1H), 2.85 (dd, J=6.1, 13.2 Hz, 1H), 2.73-2.54 (m, 3H), 2.12 (s, 3H), 1.94-1.87 (m, 2H), 1.75 (s, 2H), 1.62-1.54 (m, 2H), 1.42-1.24 (m, 2H).

10 **Example 205**

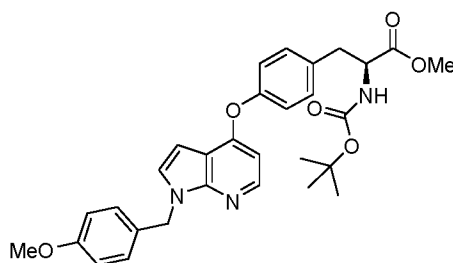
The following examples were prepared from Intermediate 204D and the boronate ester given using a procedure similar to that used for Example 204, by replacing the boronate ester given in Step E.

Ex	Structure	Boronic acid	¹ H NMR	LC-MS
205	 (S)-2-amino-3-(3-fluoro-4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide	5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole	¹ H NMR (400 MHz, DMSO) δ 12.22 (s, 1H), 8.92 (d, J=0.7 Hz, 1H), 8.12-8.09 (m, 2H), 7.83 (s, 1H), 7.65 (d, J=7.9 Hz, 1H), 7.36-7.25 (m, 2H), 7.11 (dd, J=1.3, 8.2 Hz, 1H), 6.28 (dd, J=0.8, 5.5 Hz, 1H), 3.53-3.43 (m, 1H), 3.41-3.36 (m, 1H), 2.88 (dd, J=5.9, 13.2 Hz, 1H), 2.72 (dd, J=7.6, 13.1 Hz, 1H), 2.66-2.57 (m, 2H), 2.54 (s, 1H), 2.12 (s, 3H), 1.96-1.85 (m, 3H), 1.68-1.56 (m, 2H), 1.43-1.23 (m, 2H).	Rt = 2.95 min, m/z 495.3 [M+H] ⁺ (Method 2)

Example 206**Step A****4-Bromo-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate****206A)**

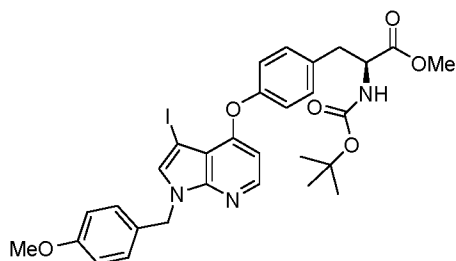
4-Bromo-7-azaindole (2.5 g, 12.69 mmol) was dissolved in DMF (20 mL) and the solution was cooled in an ice bath under a stream of nitrogen. Sodium hydride (60% in mineral oil, 635 mg, 15.88 mmol) was added and the mixture was stirred for 30 min. 4-Methoxybenzyl bromide (2.81 g, 13.96 mmol) was then added and the reaction was stirred at RT for 2 h. After that time, the mixture was quenched by the careful addition of water (30 mL) and the product was extracted into ethyl acetate (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and evaporated. The crude product was chromatographed on an 80 g Si cartridge eluting with 0-30% ethyl acetate in cyclohexane. The pure product was obtained as a cream solid (3.62 g).

LCMS (Method 4): Rt = 1.61 min, m/z 316.9/318.9 [M+H]⁺

Step B**Methyl (S)-2-(((tert-butoxycarbonyl)amino)-3-(4-((1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 206B)**

Intermediate 206B was prepared from Intermediate 206A and 1B-c according to the procedure used Step D of Example 1.

LCMS (Method 4): Rt = 1.65 min, m/z 532.1 [M+H]⁺

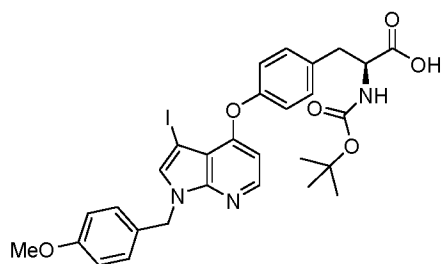
Step C

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-iodo-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate

5 **(Intermediate 206C)**

Intermediate 206C was prepared from Intermediate 206B and NIS using a procedure similar to Intermediate 186C replacing NBS with NIS.

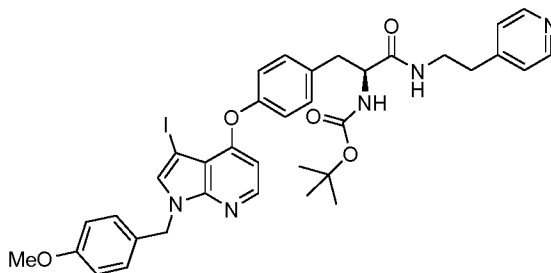
LCMS (Method 4): $R_t = 1.75$ min, m/z 658.0 $[M+H]^+$

Step D

10 **(S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-iodo-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 206D)**

Intermediate 206D was prepared from Intermediate 206C using a procedure similar to that used for Step E of Example 1.

15 LCMS (Method 4): $R_t = 1.68$ min, m/z 644.0 $[M+H]^+$

Step E

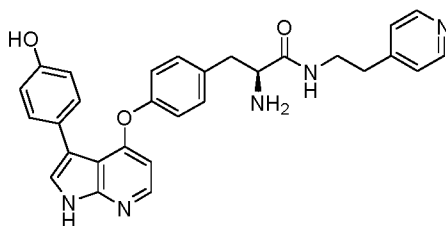
tert-butyl (S)-3-(4-((3-iodo-1-(4-methoxybenzyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-((2-(pyridin-4-yl)ethyl)amino)propan-2-yl)carbamate

(Intermediate 206E)

Intermediate 206E was prepared from Intermediate 206D and 2-(pyridin-4-yl)ethan-1-amine using a procedure similar to that used for Step F of Example 1.

LCMS (Method 4): $R_t = 1.27$ min, m/z 748.0 $[M+H]^+$

5

Step F**(S)-2-amino-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide (Example 206)**

A mixture of Intermediate 206E (170 mg, 0.228 mmol), (4-((tert-butyltrimethylsilyl)oxy)phenyl)boronic acid (115 mg, 0.456 mmol), $Pd_2Cl_2(dppf) \cdot CH_2Cl_2$ (9 mg, mmol), potassium carbonate (69 mg, mmol), DME (3 mL) and water (1 mL) was heated at 90°C for 19 h. Evaporation gave a crude product which was chromatographed on a Si cartridge (24 g) eluting with 0-10% methanol in DCM. The product was dissolved in TFA (2 mL) and stirred at 90°C for 18 h. Trifluoromethanesulfonic acid (34 mg, 0.288 mmol) was added and heating was continued at 65°C for 3 h. The reaction was allowed to cool and the poured onto an SCX-2 cartridge (5 g). After flushing with DCM and methanol, the product was eluted with 2M methanolic ammonia. Evaporation gave a crude product which was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% NH_4OH added) to give a white solid (7 mg).

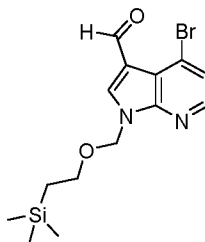
20

LCMS (Method 1): $R_t = 1.74$ min, m/z 494.1 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 11.82 (s, 1H), 9.24 (s, 1H), 8.46-8.43 (m, 2H), 8.02 (d, $J=5.5$ Hz, 1H), 7.95 (dd, $J=5.8$, 5.8 Hz, 1H), 7.45-7.40 (m, 3H), 7.26-7.19 (m, 4H), 7.06 (d, $J=8.6$ Hz, 2H), 6.71-6.68 (m, 2H), 6.25 (d, $J=5.4$ Hz, 1H), 3.39-3.27 (m, 3H), 2.88 (dd, $J=5.1$, 13.3 Hz, 1H), 2.70 (dd, $J=7.1$, 7.1 Hz, 2H), 2.60 (q, $J=7.4$ Hz, 1H), 1.69 (s, 2H).

25

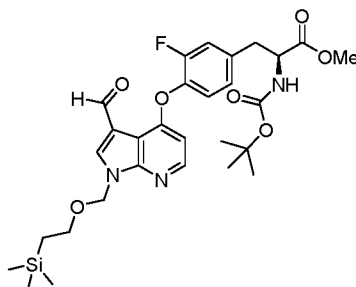
ee% (n.d.)

Example 207**Step A**

5 **4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine-3-carbaldehyde (Intermediate 207A)**

Intermediate 207A was prepared from 3-formyl-4-bromo-7-azaindole using a procedure similar to that used for the preparation of Intermediate 1C-a.

LCMS (Method 4): $R_t = 1.91$ min, m/z 355.1/357.1 $[M+H]^+$

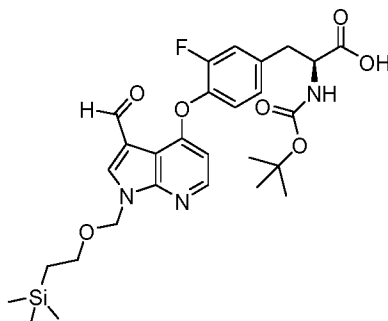
Step B

10

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-fluoro-4-((3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 207B)

15 Intermediate 207B was prepared from Intermediate 207A and Intermediate 1B-a according to the procedure in Step D of Example 1.

LCMS (Method 6): $R_t = 1.76$ min, m/z 588.4 $[M+H]^+$

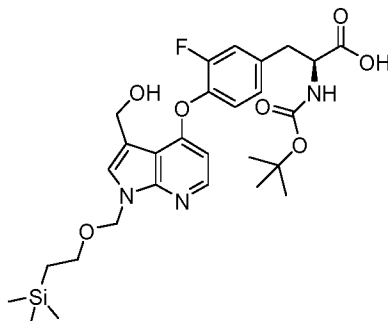
Step C

(S)-2-((tert-Butoxycarbonyl)amino)-3-(3-fluoro-4-((3-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 207C)

Intermediate 207C was prepared from Intermediate 207B using a similar procedure
5 in Step E of Example 1.

LCMS (Method 6): $R_t = 1.69$ min, m/z 574.3 $[M+H]^+$

Step D

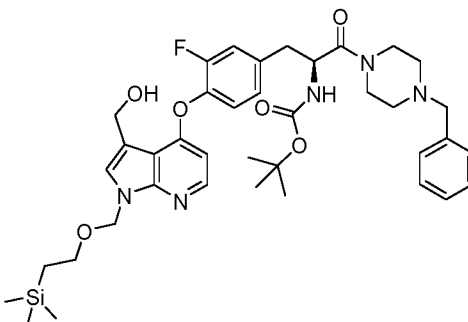


10 **(S)-2-((tert-Butoxycarbonyl)amino)-3-(3-fluoro-4-((3-(hydroxymethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 207D)**

Intermediate 207C (386 mg, 0.674 mmol) was dissolved in a mixture of DCM (10 mL) and methanol (1 mL) and sodium borohydride (26 mg, 0.684 mmol) was added. The reaction was stirred at RT overnight. A further portion of sodium borohydride (52 mg, 1.37
15 mmol) was added and stirring was continued for 2 h. the reaction mixture was washed with water (10 mL), dried (Na_2SO_4) and evaporated. The product was obtained as a cream solid (346 mg).

LCMS (Method 6): $R_t = 1.59$ min, m/z 576.3 $[M+H]^+$

Step E

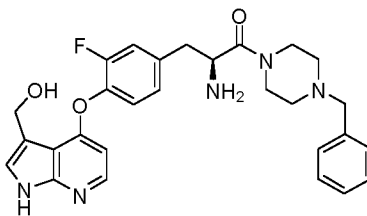


tert-Butyl (S)-(1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl)carbamate (Intermediate 207E)

Intermediate 207E was prepared from Intermediate 207D and 1-benzylpiperazine using a procedure similar to that used for step F of Example 1.

LCMS (Method 6): $R_t = 1.30$ min, m/z 734.5 $[M+H]^+$

Step F



(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (Example 207)

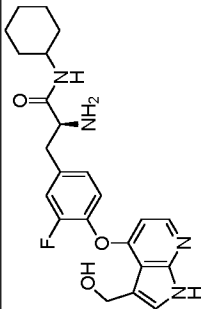
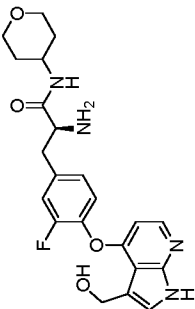
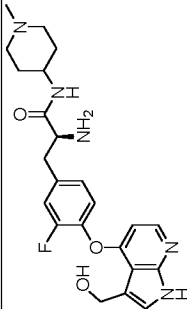
Example 207 was prepared from Intermediate 207E using a procedure similar to that used for Step G of Example 1.

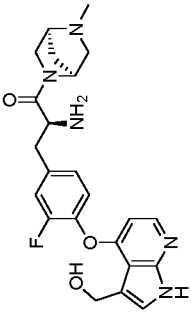
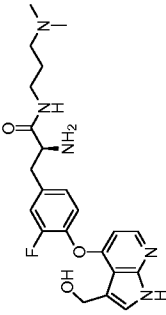
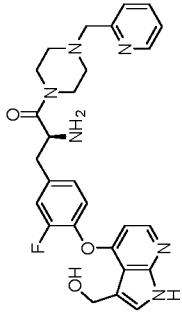
LCMS (Method 2): $R_t = 3.23$ min, m/z 504.4 $[M+H]^+$

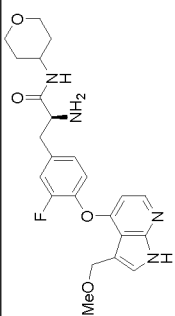
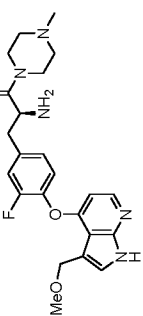
^1H NMR (400 MHz, d_6 -DMSO) δ 11.55 (s, 1H), 8.00 (d, $J=5.5$ Hz, 1H), 7.34-7.22 (m, 9H), 7.11 (dd, $J=1.3, 8.3$ Hz, 1H), 6.17 (d, $J=5.4$ Hz, 1H), 4.79-4.76 (m, 3H), 3.94 (t, $J=6.8$ Hz, 1H), 3.46-3.42 (m, 5H), 2.80 (dd, $J=6.3, 13.1$ Hz, 1H), 2.67 (dd, $J=7.4, 13.1$ Hz, 1H), 2.39-2.29 (m, 2H), 2.25-2.14 (m, 1H), 2.11-2.01 (m, 1H), 1.72-1.71 (m, 2H).

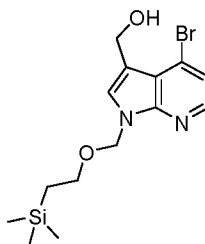
Example 208 to 215

The following examples were prepared in a similar manner example to 207 by replacing 1-benzylpiperazine in Step E the with the amine shown below.

Ex	Structure	Amine	¹ H NMR	LC-MS
208	 (S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyridol[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	Cyclohexanamine	¹ H NMR (400 MHz, d ₆ -DMSO) δ 11.57 (s, 1H), 7.99 (d, J=5.4 Hz, 1H), 7.61 (d, J=8.0 Hz, 1H), 7.31-7.20 (m, 3H), 7.12-7.07 (m, 1H), 6.17 (d, J=5.4 Hz, 1H), 4.78-4.73 (m, 3H), 3.55-3.47 (m, 1H), 3.40-3.35 (m, 1H), 2.87 (dd, J=5.9, 13.2 Hz, 1H), 2.71 (dd, J=7.3, 13.3 Hz, 1H), 1.78 (s, 2H), 1.70-1.61 (m, 4H), 1.53 (d, J=12.2 Hz, 1H), 1.31-1.06 (m, 5H).	Rt = 3.11 min, m/z 427.4 [M+H] ⁺ (Method 2)
209	 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyridol[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide (ee% n.d.)	Tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.54 (s, 1H), 8.00 (d, J=5.4 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.29-7.22 (m, 3H), 7.09 (dd, J=1.3, 8.3 Hz, 1H), 6.17 (dd, J=0.9, 5.4 Hz, 1H), 4.78-4.73 (m, 3H), 3.83-3.71 (m, 3H), 3.42-3.35 (m, 2H), 2.88 (dd, J=5.9, 13.2 Hz, 1H), 2.72 (dd, J=7.5, 13.2 Hz, 1H), 1.76 (s, 2H), 1.66-1.57 (m, 2H), 1.44-1.22 (m, 2H).	Rt = 1.74 min, m/z 429.0 [M+H] ⁺ (Method 1)
210	 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyridol[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide	1-Methylpiperidin-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.56 (d, J=1.5 Hz, 1H), 8.00 (d, J=5.4 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.29-7.23 (m, 3H), 7.09 (dd, J=1.3, 8.3 Hz, 1H), 6.18 (dd, J=0.8, 5.5 Hz, 1H), 4.75 (s, 3H), 3.52-3.42 (m, 2H), 2.90 (dd, J=6.1, 13.3 Hz, 1H), 2.79-2.60 (m, 3H), 2.15 (s, 3H), 1.99-1.91 (m, 2H), 1.68-1.56 (m, 2H), 1.46-1.23 (m, 2H).	Rt = 2.44 min, m/z 442.2 [M+H] ⁺ (Method 2)

Ex	Structure	Amine	¹ H NMR	LC-MS
211	 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one	(1S,4S)-2-Methyl-2,5-diazabicyclo[2.2.1]heptane	¹ H NMR (400 MHz, DMSO) δ 11.58-11.53 (m, 1H), 8.01 (dd, J=3.1, 5.4 Hz, 1H), 7.37-7.22 (m, 3H), 7.13 (dd, J=2.0, 8.2 Hz, 1H), 6.25-6.14 (m, 1H), 4.79-4.72 (m, 3H), 4.50-4.22 (m, 1H), 3.78-3.50 (m, 1H), 3.38-3.35 (m, 2H), 3.15-3.00 (m, 1H), 2.81-2.65 (m, 3H), 2.27 (s, 1H), 2.15 (s, 3H), 1.72 (dd, J=8.9, 8.9 Hz, 1H), 1.50-1.28 (m, 1H).	Rt = 2.29 min, m/z 440.2 [M+H] ⁺ (Method 2)
212	 (S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide	N,N-Dimethylpropane-1,3-diamine	¹ H NMR (400 MHz, DMSO) δ 11.55 (d, J=1.2 Hz, 1H), 8.00 (d, J=5.4 Hz, 1H), 7.87 (dd, J=5.7, 5.7 Hz, 1H), 7.29-7.22 (m, 3H), 7.10 (dd, J=1.3, 8.3 Hz, 1H), 6.18-6.16 (m, 1H), 4.75 (s, 3H), 3.43-3.37 (m, 2H), 3.12-3.00 (m, 2H), 2.92 (dd, J=5.7, 13.3 Hz, 1H), 2.75-2.67 (m, 1H), 2.17-2.10 (m, 3H), 2.09 (s, 6H), 1.51-1.42 (m, 2H).	Rt = 2.42 min, m/z 430.2 [M+H] ⁺ (Method 2)
213	 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one	1-(Pyridin-2-ylmethyl)piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 11.56-11.56 (m, 1H), 8.49 (dd, J=0.9, 4.9 Hz, 1H), 8.01 (d, J=5.4 Hz, 1H), 7.79-7.74 (m, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.34-7.22 (m, 4H), 7.11 (dd, J=1.3, 8.3 Hz, 1H), 6.19-6.17 (m, 1H), 4.82-4.74 (m, 3H), 3.94 (dd, J=6.9, 6.9 Hz, 1H), 3.58 (s, 2H), 3.54-3.37 (m, 4H), 2.80 (dd, J=6.4, 13.2 Hz, 1H), 2.71-2.64 (m, 1H), 2.42-2.23 (m, 3H), 2.18-2.07 (m, 1H), 1.79-1.75 (m, 2H).	Rt = 1.57 min, m/z 505.2 [M+H] ⁺ (Method 1)

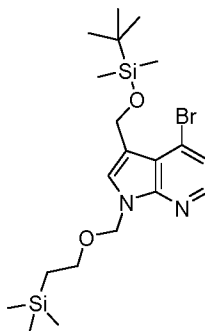
Ex	Structure	Amine	¹ H NMR	LC-MS
214	 Isolated from the preparation of Example 211 (ee% n.d.) (S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide	Tetrahydro-2H-pyran-4-amine	¹ H NMR (400 MHz, DMSO) δ 11.73 (s, 1H), 8.24 (s, 1H), 8.03 (d, J=5.4 Hz, 1H), 7.82 (d, J=7.8 Hz, 1H), 7.41 (d, J=2.1 Hz, 1H), 7.30-7.22 (m, 2H), 7.09 (dd, J=1.2, 8.3 Hz, 1H), 6.22 (d, J=4.8 Hz, 1H), 4.61 (s, 2H), 3.82-3.70 (m, 4H), 3.45 (dd, J=6.8, 6.8 Hz, 1H), 3.38-3.28 (m, 3H), 3.25 (s, 3H), 2.90 (dd, J=6.1, 13.3 Hz, 1H), 2.76 (dd, J=7.4, 13.3 Hz, 1H), 1.69-1.54 (m, 2H), 1.44-1.23 (m, 2H).	LC-MS Rt = 2.07 min, m/z 443.1 [M+H] ⁺ (Method 1)
215	 Isolated product when synthesizing hydroxyalkyl derivative on R₁ (ee% n.d.) (S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one	1-Methyl-piperazine	¹ H NMR (400 MHz, DMSO) δ 11.70 (s, 1H), 8.03 (d, J=5.5 Hz, 1H), 7.40 (s, 1H), 7.31 (dd, J=2.1, 12.0 Hz, 1H), 7.24 (dd, J=8.4, 8.4 Hz, 1H), 7.11 (dd, J=1.4, 8.3 Hz, 1H), 6.23-6.21 (m, 1H), 4.61 (s, 2H), 3.95 (dd, J=6.9, 6.9 Hz, 1H), 3.56-3.49 (m, 1H), 3.46-3.36 (m, 3H), 3.25 (s, 3H), 2.80 (dd, J=6.6, 13.2 Hz, 1H), 2.72-2.65 (m, 1H), 2.28 (dd, J=3.5, 10.4 Hz, 2H), 2.14 (s, 3H), 2.10-1.89 (m, 2H), 1.74 (s, 2H).	LC-MS Rt = 1.56 min, m/z 442.1 [M+H] ⁺ (Method 1)

Example 213 (Alternative method)**Step A**

5 **(4-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)methanol (Intermediate 213A)**

Intermediate 213A was prepared from Intermediate 207A using a procedure similar to that used for the preparation of Intermediate 207D.

LCMS (Method 4): $R_t = 1.58$ min, m/z 357.1/359.1 $[M+H]^+$

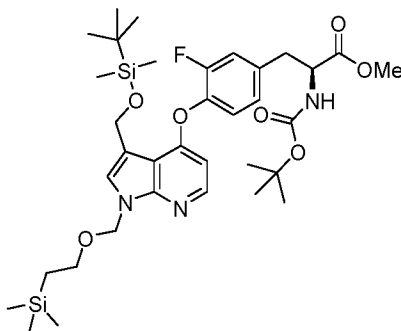
Step B

10

4-Bromo-3-(((tert-butyl)dimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 213B)

Intermediate 213A (204 mg, 0.57 mmol) in DCM (6.5 mL) was treated with imidazole (78 mg, 1.14 mmol). *tert*-Butyldimethylsilyl chloride (102 mg, 0.68 mmol) was added and the reaction was stirred at RT overnight. The reaction mixture was diluted with water (10 mL) and the DCM layer was separated. The aqueous was further extracted with DCM (10 mL) and the combined extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed on a 25 g Si cartridge eluting with 0-30% ethyl acetate in cyclohexane to give the desired product as colourless oil (240 mg).

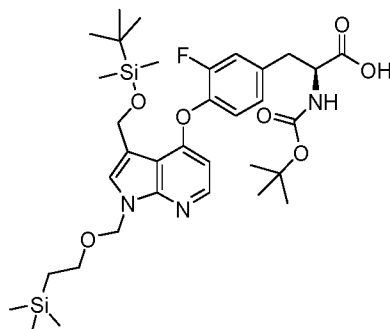
20 LCMS (Method 4): $R_t = 2.19$ min, m/z 471.2/473.2 $[M+H]^+$

Step C

- Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-(((tert-butyl)dimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)propanoate (Intermediate 213C)**

Intermediate 213C was prepared from Intermediate 213B and Intermediate 1B-a according to the procedure in Step D of Example 1.

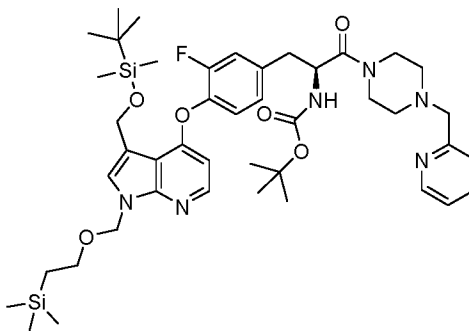
LCMS (Method 4): $R_t = 4.55$ min, m/z 704.5 $[M+H]^+$

Step D

- (S)-2-((tert-Butoxycarbonyl)amino)-3-(4-((3-(((tert-butyl)dimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)propanoic acid (Intermediate 213D)**

Intermediate 213D was prepared from Intermediate 213C using a procedure in Step E of Example 1.

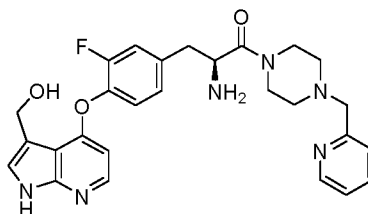
LCMS (Method 4): $R_t = 4.39$ min, m/z 690 $[M+H]^+$

Step E

tert-Butyl (S)-(3-(4-((3-(((tert-butyldimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-1-oxo-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-2-yl)carbamate (Intermediate 213E)

Intermediate 213E was prepared from Intermediate 213D and 1-(pyridin-2-ylmethyl)piperazine using a procedure similar to that used for Step F of Example 1.

LCMS (Method 4): $R_t = 3.33$ min, m/z 849.5 $[M+H]^+$

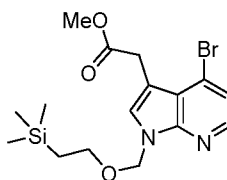
Step F

(S)-2-Amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one (Example 213)

Example 213 was prepared from Intermediate 213E using a procedure similar to that used for Step G of Example 1.

LCMS (Method 1): $R_t = 1.57$ min, m/z 505.2 $[M+H]^+$

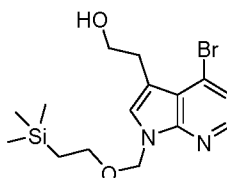
1H NMR (400 MHz, d_6 -DMSO) δ 11.56-11.56 (m, 1H), 8.49 (dd, $J=0.9, 4.9$ Hz, 1H), 8.01 (d, $J=5.4$ Hz, 1H), 7.79-7.74 (m, 1H), 7.44 (d, $J=7.8$ Hz, 1H), 7.34-7.22 (m, 4H), 7.11 (dd, $J=1.3, 8.3$ Hz, 1H), 6.19-6.17 (m, 1H), 4.82-4.74 (m, 3H), 3.94 (dd, $J=6.9, 6.9$ Hz, 1H), 3.58 (s, 2H), 3.54-3.37 (m, 4H), 2.80 (dd, $J=6.4, 13.2$ Hz, 1H), 2.71-2.64 (m, 1H), 2.42-2.23 (m, 3H), 2.18-2.07 (m, 1H), 1.79-1.75 (m, 2H).

Example 216**Step A**

5 **Methyl 2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate (Intermediate 216A)**

Intermediate 216A was prepared from methyl 2-(4-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)acetate using a method similar to that used for Intermediate 1C-a.

LCMS (Method 4): $R_t = 1.70$ min, m/z 399.1/401.1 $[M+H]^+$

Step B

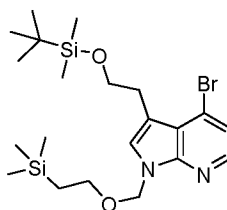
10

2-(4-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-ol (Intermediate 216B)

Intermediate 216B was prepared from Intermediate 216A using a method similar to that used in the preparation of Intermediate 207D.

15

LCMS (Method 4): $R_t = 1.64$ min, m/z 371.0/373.0 $[M+H]^+$

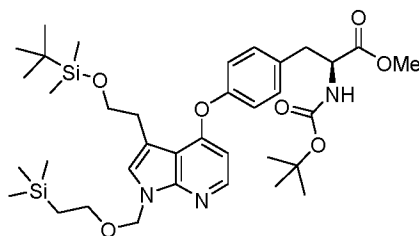
Step C

4-Bromo-3-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine (Intermediate 216C)

20

Intermediate 216C was prepared from Intermediate 216B using a method similar to that used in the preparation of Intermediate 213B.

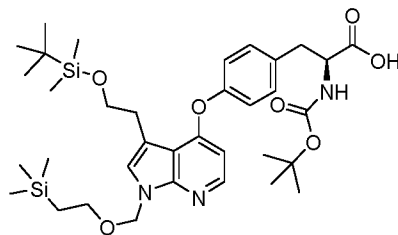
LCMS (Method 4): $R_t = 2.27$ min, m/z 485.0/487.0 $[M+H]^+$

Step D

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoate (Intermediate 216D)

Intermediate 216D was prepared from Intermediate 216C and Intermediate 1B-c using a procedure similar to Step D of Example 1.

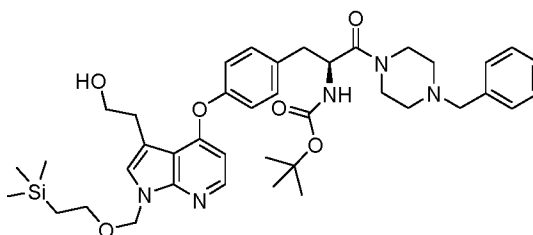
LCMS (Method 4): $R_t = 2.11$ min, m/z 700.5 $[M+H]^+$

Step E

(S)-2-((tert-butoxycarbonyl)amino)-3-(4-((3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoic acid (Intermediate 216E)

Intermediate 216E was prepared from Intermediate 216D using a procedure analogous to that used in Step E of Example 1.

LCMS (Method 4): $R_t = 2.08$ min, m/z 686.5 $[M+H]^+$

Step F

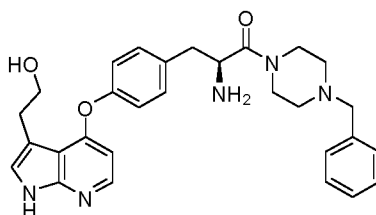
tert-Butyl (S)-(1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2-hydroxyethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-

oxopropan-2-yl)carbamate (Intermediate 216F)

Intermediate 216F was prepared from Intermediate 216E and 1-benzylpiperazine using a method similar to that of Step D of Example 1.

LCMS (Method 4): $R_t = 2.29$ min, m/z 730.7 $[M+H]^+$

5

Step G

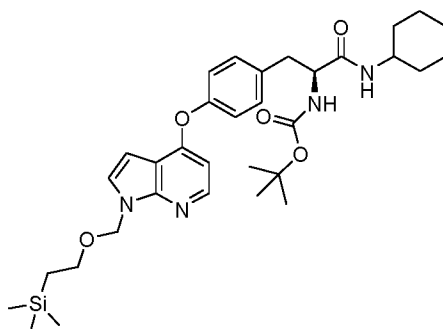
(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one (Example 216)

Example 216 was synthesized from Intermediate 216F as described for Step G of Example 1.

LCMS (Method 1): $R_t = 1.71$ min, m/z 500.2 $[M+H]^+$

1H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 7.98 (d, $J=5.4$ Hz, 1H), 7.33-7.24 (m, 7H), 7.16 (d, $J=2.2$ Hz, 1H), 7.08 (d, $J=8.5$ Hz, 2H), 6.21 (d, $J=5.4$ Hz, 1H), 4.53 (dd, $J=5.2$, 5.2 Hz, 1H), 3.91 (dd, $J=6.8$, 6.8 Hz, 1H), 3.71-3.63 (m, 2H), 3.45-3.42 (m, 6H), 2.95-2.89 (m, 2H), 2.78 (dd, $J=6.8$, 13.1 Hz, 1H), 2.66 (dd, $J=6.6$, 12.7 Hz, 1H), 2.35-2.29 (m, 2H), 2.22-2.17 (m, 1H), 2.03 (s, 1H), 1.77 (s, 2H).

15

Example 217**Step A**

20

tert-Butyl

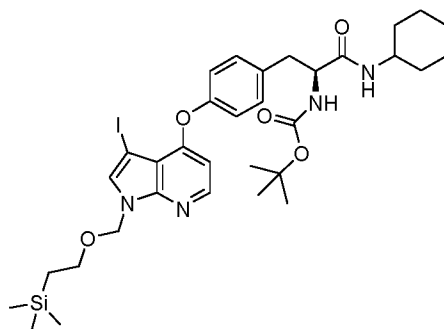
(S)-1-(cyclohexylamino)-1-oxo-3-(4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-2-

yl)carbamate (Intermediate 217A)

Intermediate 217A was prepared from Intermediate 1E-e and cyclohexanamine using the same procedure as for Step F of Example 1.

LCMS (Method 5): $R_t = 1.91$ min, m/z 609.4 $[M+H]^+$

5

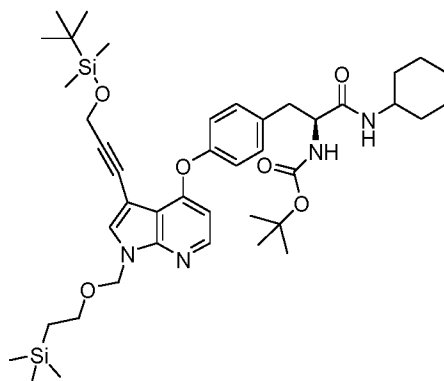
Step B

tert-Butyl (S)-(1-(cyclohexylamino)-3-(4-((3-iodo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl)carbamate (Intermediate 217B)

10

Intermediate 217B was prepared from Intermediate 217A using the same procedure as for Intermediate 186C by substituting NBS with NIS.

LCMS (Method 4): $R_t = 2.27$ min, m/z 735.4 $[M+H]^+$

Step C

15

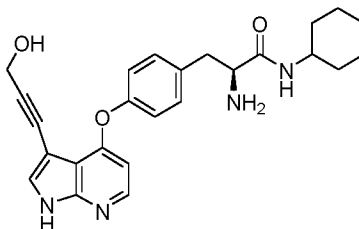
tert-Butyl (S)-(3-(4-((3-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)carbamate (Intermediate 217C)

Intermediate 217B (390 mg, 0.531 mmol), tert-butyldimethyl(prop-2-yn-1-yloxy)silane (181 mg, 1.06 mmol), $\text{PdCl}_2(\text{dppf})_2$, CH_2Cl_2 (22 mg, 0.027 mmol), copper (I)

iodide (10 mg, 0.053 mmol) and trimethylamine (739 mL, 5.32 mmol) in THF (10 mL) were sealed in a reaction tube and the vessel was purged with argon for 5 min. The mixture was heated at 90°C overnight and then allowed to cool to RT. The mixture was concentrated *in vacuo* and chromatographed on a 24 g Si cartridge eluting with 0-30% ethyl acetate in cyclohexane. The product was obtained as a cream solid (410 mg)

LCMS (Method 6): $R_t = 2.18$ min, m/z 777.6 $[M+H]^+$

Step D



(S)-2-amino-N-cyclohexyl-3-(4-((3-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide (Example 217)

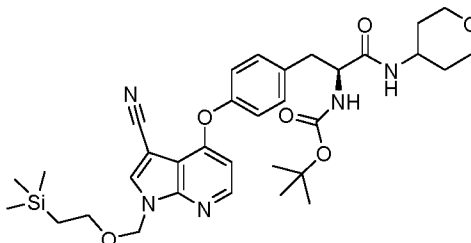
Example 217 was prepared from Intermediate 217C using a procedure similar to that used for Step G of Example 1.

LCMS (Method 2): $R_t = 3.25$ min, m/z 433.1 $[M+H]^+$

1H NMR (400 MHz, d_6 -DMSO) δ 12.09 (s, 1H), 8.07 (d, $J=5.5$ Hz, 1H), 7.69 (s, 1H), 7.59 (d, $J=8.1$ Hz, 1H), 7.27 (d, $J=8.6$ Hz, 2H), 7.07 (d, $J=8.5$ Hz, 2H), 6.32 (d, $J=5.4$ Hz, 1H), 5.16 (s, 1H), 4.20 (s, 2H), 3.55 - 3.47 (m, 1H), 3.36 (dd, $J=5.8, 7.4$ Hz, 1H), 2.87 (dd, $J=5.7, 13.3$ Hz, 1H), 2.67 (dd, $J=7.8, 13.2$ Hz, 1H), 1.84 (s, 2H), 1.72 - 1.48 (m, 4H), 1.29 - 1.05 (m, 6H).

Example 218

Step A



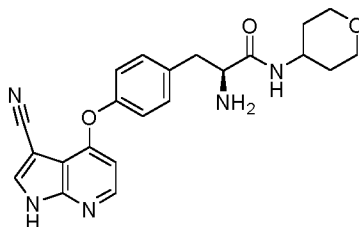
tert-Butyl (S)-3-(4-((3-cyano-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-

pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-((tetrahydro-2H-pyran-4-yl)amino)propan-2-yl)carbamate (Intermediate 218A)

Intermediate 189A (122 mg, 0.177 mmol), zinc cyanide (13 mg, 0.111 mmol), Pd₂(dba)₃ (8 mg, 0.009 mmol), 1,1'-ferrocenediylbis(diphenylphosphine) (12 mg, 0.022 mmol), and water (5 drops) in DMF (3 mL) was heated at 125°C overnight. The mixture was allowed to cool and then partitioned between ethyl acetate (10 mL) and brine (8 mL). The organic layer was separated, dried (Na₂SO₄) and evaporated. The crude product (160 mg) was used in the next step without further purification.

LCMS (Method 8): Rt = 1.65 min, m/z 636.4 [M+H]⁺

Step B



(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide (Example 218)

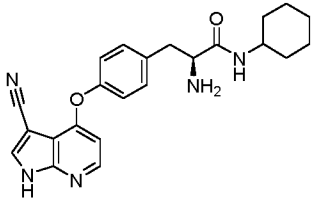
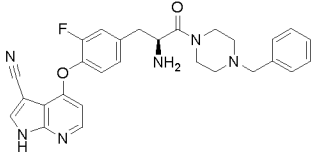
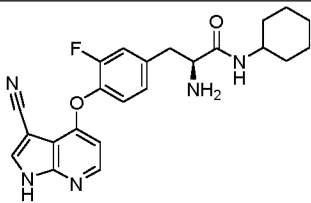
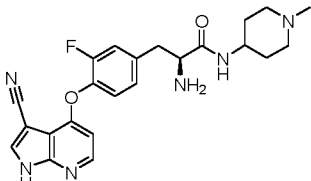
Example 218 was prepared from Intermediate 218A using a procedure similar to that for Step G of Example 1.

LCMS (Method 1): Rt = 2.26 min, m/z 406.2 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 8.38 (s, 1H), 8.19 (d, J=5.5 Hz, 1H), 7.72 (d, J=7.8 Hz, 1H), 7.32 (d, J=8.6 Hz, 2H), 7.16 (d, J=8.6 Hz, 2H), 6.40 (d, J=5.5 Hz, 1H), 3.83-3.71 (m, 3H), 3.41-3.36 (m, 3H), 2.89 (dd, J=5.8, 13.2 Hz, 1H), 2.72 (dd, J=7.6, 13.2 Hz, 1H), 1.67-1.55 (m, 2H), 1.43-1.27 (m, 2H).

Example 219 to 222

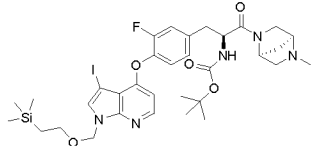
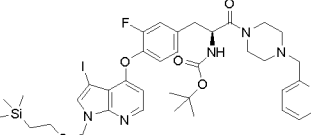
The following examples were prepared in two step synthesis in a similar manner of Example 218 from the starting materials shown.

Ex	Structure	Starting material	¹ H NMR	LC-MS
219	 (ee% = 87%) (S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide	Intermediate 217B	¹ H NMR (400 MHz, d ₆ -DMSO) δ 8.37 (s, 1H), 8.18 (d, J=5.5 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.32 (d, J=8.6 Hz, 2H), 7.16 (d, J=8.6 Hz, 2H), 6.39 (d, J=5.5 Hz, 1H), 3.55-3.47 (m, 1H), 3.41-3.35 (m, 1H), 2.89 (dd, J=5.7, 13.2 Hz, 1H), 2.70 (dd, J=7.6, 13.3 Hz, 1H), 1.70-1.57 (m, 4H), 1.55-1.47 (m, 1H), 1.30-1.16 (m, 2H), 1.14-1.03 (m, 3H).	Rt = 2.79 min, m/z 404.3 [M+H] ⁺ (Method 1)
220	 (ee% n.d.) (S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile	Intermediate 187C	¹ H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 8.20 (d, J=5.5 Hz, 1H), 7.37-7.29 (m, 6H), 7.29-7.23 (m, 2H), 7.16 (dd, J=1.2, 8.3 Hz, 1H), 6.39 (d, J=4.8 Hz, 1H), 3.95 (t, J=6.9 Hz, 1H), 3.54-3.39 (m, 8H), 2.82 (dd, J=6.1, 13.2 Hz, 1H), 2.69 (dd, J=7.5, 13.2 Hz, 1H), 2.39-2.29 (m, 2H), 2.24-2.15 (m, 1H), 2.12-2.02 (m, 1H).	Rt = 2.15 min, m/z 499.3 [M+H] ⁺ (Method 1)
221	 (S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide	Intermediate 186C	¹ H NMR (400 MHz, d ₆ -DMSO) δ 8.42 (s, 1H), 8.20 (d, J=5.6 Hz, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.36 (t, J=8.4 Hz, 1H), 7.31 (dd, J=1.9, 11.7 Hz, 1H), 7.14 (dd, J=1.2, 8.3 Hz, 1H), 6.39 (d, J=4.8 Hz, 1H), 3.56-3.47 (m, 1H), 3.44-3.37 (m, 2H), 2.90 (dd, J=5.8, 13.2 Hz, 1H), 2.73 (dd, J=7.5, 13.2 Hz, 1H), 1.70-1.49 (m, 6H), 1.30-1.07 (m, 6H).	Rt = 2.79 min, m/z 422.2 [M+H] ⁺ (Method 1)
222	 (S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-(1-methylpiperidin-4-yl)propanamide	Intermediate 204D	¹ H NMR (400 MHz, DMSO) δ 8.39 (s, 1H), 8.18 (d, J=5.5 Hz, 1H), 7.66 (d, J=7.9 Hz, 1H), 7.37-7.28 (m, 2H), 7.13 (dd, J=1.3, 8.3 Hz, 1H), 6.38 (dd, J=0.8, 5.5 Hz, 1H), 3.53-3.44 (m, 1H), 3.39 (dd, J=6.0, 7.4 Hz, 2H), 2.89 (dd, J=5.8, 13.3 Hz, 1H), 2.72 (dd, J=7.6, 13.3 Hz, 1H), 2.66-2.58 (m, 2H), 2.12 (s, 3H), 1.96-1.87 (m, 2H), 1.68-1.57 (m, 2H), 1.43-1.23 (m, 2H).	Rt = 1.74 min, m/z 437.1 [M+H] ⁺ (Method 1)

Examples 223 to 224**Preparation of Intermediates 223A to 224B**

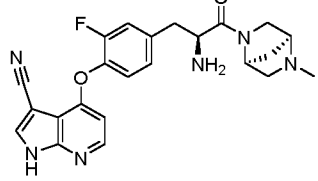
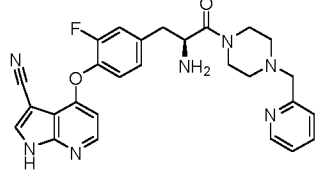
The following intermediates were prepared from Intermediate 204C and the amine indicated in a similar way as reported for Step F of Example 1.

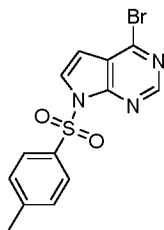
5

Intermediate	Structure	Amine	LC-MS
223A		(1S,4S)-2-methyl-2,5-diazabicyclo[2.2.1]-heptane	Rt = 2.83 min, m/z 766.1 [M+H] ⁺ (Method 9)
224A		1-(pyridin-2-ylmethyl)piperazine	Rt = 3.19 min, m/z 831.3 [M+H] ⁺ (Method 9)

Preparation of Example

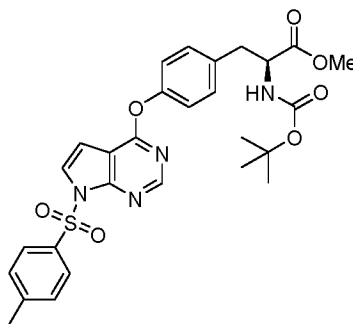
The following examples were prepared in two step synthesis in a similar manner of Example 218 from the starting materials shown.

Ex	Structure	Amine	¹ H NMR	LC-MS
223	 4-((S)-2-amino-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile	Intermediate 223A	¹ H NMR (400 MHz, DMSO) δ 8.41 (d, J=2.7 Hz, 1H), 8.23-8.20 (m, 1H), 7.41-7.31 (m, 2H), 7.19-7.14 (m, 1H), 6.47-6.34 (2xm, 1H), 4.51-31 (2xs, 1H), 3.70-3.55 (2xt, J=7.2 Hz, 1H), 3.39 – 3.33 (m, 4H), 3.14 – 3.00 (2xd, J=10.1 Hz, 1H), 2.84-2.65 (m, 3H), 2.28-2.26 (2xs, 3H), 1.76-1.68 (m, 1H), 1.57-1.25 (m, 1H).	Rt = 1.73 min, m/z 435.0 [M+H] ⁺ (Method 1)
224	 (S)-4-(4-(2-amino-3-oxo-3-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile	Intermediate 224A	¹ H NMR (400 MHz, DMSO) δ 8.50-8.48 (m, 1H), 8.42 (s, 1H), 8.22 (d, J=5.6 Hz, 1H), 7.79-7.74 (m, 1H), 7.44 (d, J=7.8 Hz, 1H), 7.40-7.33 (m, 2H), 7.29-7.24 (m, 1H), 7.16 (dd, J=1.1, 8.3 Hz, 1H), 6.40 (d, J=5.1 Hz, 1H), 3.96 (dd, J=6.8, 6.8 Hz, 1H), 3.59 (s, 2H), 3.56-3.40 (m, 5H), 2.84 (dd, J=6.0, 13.2 Hz, 1H), 2.72-2.64 (m, 1H), 2.47-2.21 (m, 5H).	Rt = 1.96 min, m/z 500.3 [M+H] ⁺ (Method 1)

Example 225**Step A****4-Bromo-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (Intermediate 225A)**

5 Intermediate 225A was prepared similarly to Intermediate 131A-a from 4-bromo-7H-pyrrolo[2,3-d]pyrimidine.

LCMS (Method 7): $R_t = 3.82$ min, m/z 351.9/353.9 $[M+H]^+$

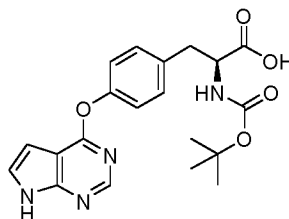
Step B

10 **Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-((7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propanoate (Intermediate 225B)**

Intermediate 225B was prepared from Intermediate 225A and 1B-c using a method similar to that used in Step D of Example 1.

LCMS (Method 5): $R_t = 1.73$ min, m/z 567.3 $[M+H]^+$

15 **Step C**



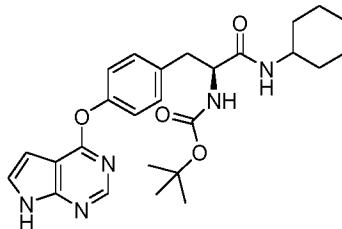
(S)-2-tert-Butoxycarbonylamino-3-{4-[7-(toluene-4-sulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy]phenyl}propionic acid (Intermediate 225C)

Intermediate 225B (406 mg, 1.02 mmol) was dissolved in methanol and 2M lithium

hydroxide solution was added. The reaction was stirred at RT overnight. The methanol was evaporated *in vacuo* and the resulting aqueous solution was acidified to pH 5 by the addition of 1N HCl. The product was extracted into DCM (3 x 8 mL) and the combined extracts were dried (Na₂SO₄) and evaporated. The product was obtained as a cream solid (299 mg).

5 LCMS (Method 5): Rt = 1.29 min, m/z 399.2 [M+H]⁺

Step D

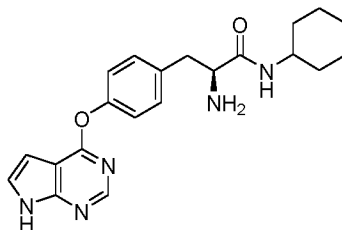


tert-Butyl (S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl carbamate (Intermediate 225D)

10 Intermediate 225D was prepared from Intermediate 225C and cyclohexanamine using a procedure similar to step F of Example 1.

LCMS (Method 6): Rt = 1.43 min, m/z 480.4 [M+H]⁺

Step E



15 **(S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide (Example 225)**

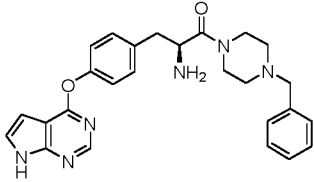
Example 225 was prepared from Intermediate 225D using a procedure similar to Step G of Example 1.

LCMS (Method 1): Rt = 2.82 min, m/z 380.2 [M+H]⁺

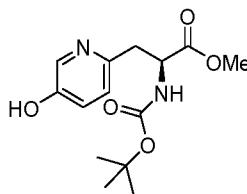
20 ¹H NMR (400 MHz, d₆-DMSO) δ 12.19 (s, 1H), 8.28 (s, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.44 (d, J=3.5 Hz, 1H), 7.27 (d, J=8.6 Hz, 2H), 7.14 (d, J=8.6 Hz, 2H), 6.41 (d, J=3.5 Hz, 1H), 3.57-3.47 (m, 1H), 3.40-3.35 (m, 1H), 2.90 (dd, J=5.5, 13.3 Hz, 1H), 2.66 (dd, J=7.8, 13.3 Hz, 1H), 1.72-1.62 (m, 5H), 1.54 (dd, J=3.6, 8.9 Hz, 1H), 1.29-1.05 (m, 6H).

Example 226

The following example was prepared in a similar way of Example 225, by replacing the amine in Step D with that indicated in the table.

Ex	Structure	Amine	¹ H NMR	LC-MS
226	 (S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one	1-Benzyl-piperazine	¹ H NMR (400 MHz, d6-DMSO) δ 12.20 (s, 1H), 8.28 (s, 1H), 7.45 (d, J=3.5 Hz, 1H), 7.35-7.21 (m, 7H), 7.14 (d, J=8.6 Hz, 2H), 6.44 (d, J=3.5 Hz, 1H), 3.92 (t, J=6.9 Hz, 1H), 3.47-3.41 (m, 6H), 2.79 (dd, J=6.7, 13.1 Hz, 1H), 2.67 (dd, J=7.2, 13.2 Hz, 1H), 2.32-2.24 (m, 3H), 2.12-2.05 (m, 1H), 1.77-1.77 (m, 2H).	Rt = 2.08 min, m/z 457.3 [M+H] ⁺ (Method 1)

5

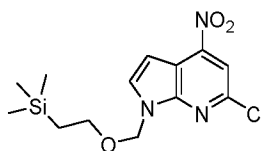
Example 227**Step A**

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-hydroxypyridin-2-yl)propanoate (Intermediate 227A)

10

Intermediate 227A was prepared from methyl (S)-2-amino-3-(5-hydroxypyridin-2-yl)propanoate hydrochloride using a method similar to that of Step B of Example 1.

LCMS (Method 6): Rt = 0.86 min, m/z 297.1 [M+H]⁺

Step B

15

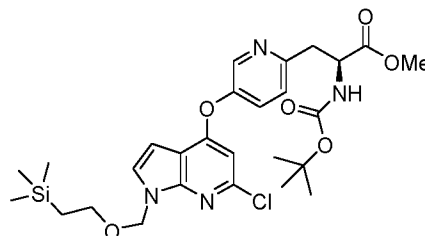
6-Chloro-4-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridine

b)pyridine (Intermediate 227B)

Intermediate 227B was prepared from 6-chloro-4-nitro-1H-pyrrolo[2,3-b]pyridine using a method similar to that of Step C of Example 1.

LCMS (Method 6): $R_t = 4.71$ min

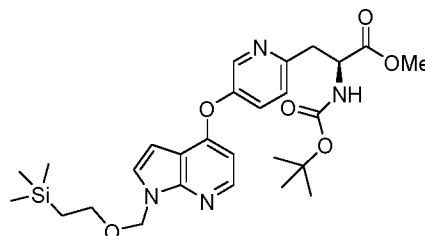
¹H NMR (400 MHz, DMSO) δ 7.99 (s, 1H), 7.68 (d, $J=3.5$ Hz, 1H), 7.24 (d, $J=3.5$ Hz, 1H), 5.75 (s, 2H), 3.60 (m, 2H), 0.98 (m, 2H), 0.00 (s, 9H).

Step C

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-((6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)propanoate (Intermediate 227C)

Intermediate 227B (302 mg, 0.924 mmol), Intermediate 227A (273 mg, 0.922 mmol) and potassium carbonate (382 mg, 2.77 mmol) were heated at 120°C in DMSO (5 mL) for 2 h. The reaction mixture was allowed to cool and then poured into water (15 mL). The product was extracted into ethyl acetate (3 x 10 mL) and the combined extracts were dried (Na₂SO₄) and evaporated. Pure product was obtained by chromatography on a Si cartridge (24 g) eluting with 0-40% ethyl acetate in cyclohexane. The product was a cream solid (320 mg).

LCMS (Method 6): $R_t = 1.85$ min, m/z 577.3 [M+H]⁺

Step D

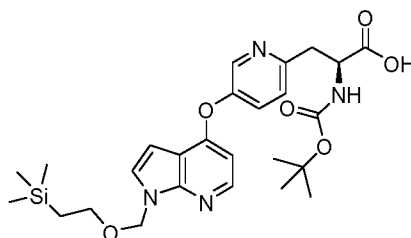
Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(5-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)propanoate (Intermediate 227D)

(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)propanoate (Intermediate 227D)

A solution of Intermediate 227C (320 mg, 0.556 mmol) and trimethylamine (93 μ L, 0.663 mmol) in IMS (20 mL) was stirred over 10% palladium on carbon (32 mg) under a blanket of hydrogen gas. After 18 h at RT the mixture was filtered through Celite[®] and the solvent was evaporated to give the desired product as a cream solid (309 mg).

LCMS (Method 4): Rt = 1.96 min, m/z 543.3 [M+H]⁺

Step E

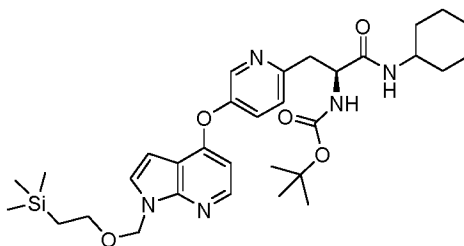


(S)-2-(((tert-Butoxycarbonyl)amino)-3-(5-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)propanoic acid (Intermediate 227E)

Intermediate 227E was prepared from Intermediate 227D according to the procedure described in Step E of Example 1.

LCMS (Method 6): Rt = 1.65 min, m/z 529.3 [M+H]⁺

Step F

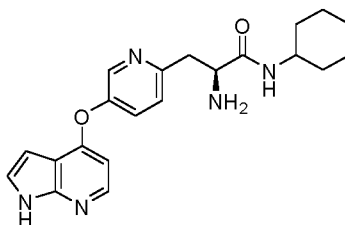


tert-Butyl (S)-1-(cyclohexylamino)-1-oxo-3-(5-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)propan-2-yl)carbamate (Intermediate 227F)

Intermediate 227F was prepared from Intermediate 227E and cyclohexanamine using a method analogous to in Step F of Example 1.

LCMS (Method 6): Rt = 1.79 min, m/z 610.4 [M+H]⁺

Step G



(S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-N-

5 cyclohexylpropanamide (Example 227)

Example 227 was prepared from Intermediate 227F using a method analogous to that used for Step G of Example 1.

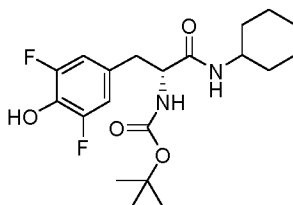
LCMS (Method 1): Rt = 2.36 min, m/z 380.2 [M+H]⁺

¹H NMR (400 MHz, DMSO) δ 11.80 (s, 1H), 8.42 (d, J=2.7 Hz, 1H), 8.09 (d, J=5.4 Hz, 1H), 7.67 (d, J=8.1 Hz, 1H), 7.56 (dd, J=2.9, 8.5 Hz, 1H), 7.38 (d, J=3.6 Hz, 1H), 7.33 (d, J=8.5 Hz, 1H), 6.43 (d, J=5.4 Hz, 1H), 6.24 (d, J=3.5 Hz, 1H), 3.57-3.47 (m, 2H), 3.05 (dd, J=5.3, 13.4 Hz, 1H), 2.83 (dd, J=8.2, 13.4 Hz, 1H), 1.83 (s, 2H), 1.72-1.59 (m, 3H), 1.58-1.49 (m, 1H), 1.28-1.06 (m, 6H).

Example 228

15 The following example was prepared in a similar way of Example 227, by replacing in Step F the amine indicated in the table.

Ex	Structure	Amine	¹ H NMR	LC-MS
228	(S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one	1-Benzyl-piperazine	¹ H NMR (400 MHz, DMSO) δ 11.81 (s, 1H), 8.42 (d, J=2.7 Hz, 1H), 8.10 (d, J=5.4 Hz, 1H), 7.56 (dd, J=2.9, 8.5 Hz, 1H), 7.41-7.36 (m, 1H), 7.36-7.22 (m, 8H), 6.44 (d, J=5.4 Hz, 1H), 6.23 (d, J=2.6 Hz, 1H), 4.10 (dd, J=5.7, 7.8 Hz, 1H), 3.55-3.37 (m, 4H), 2.96 (dd, J=5.6, 13.5 Hz, 1H), 2.78 (dd, J=8.0, 13.5 Hz, 1H), 2.39-2.18 (m, 4H), 1.78 (s, 2H).	Rt = 1.77 min, m/z 457.3 [M+H] ⁺ (Method 1)

Example 229**Step A**

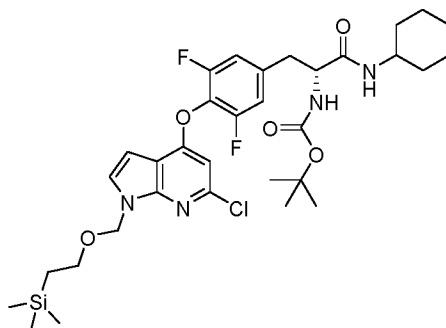
tert-butyl (R)-2-((tert-butoxycarbonyl)amino)-3-(3,5-difluoro-4-hydroxyphenyl)-1-

5 **oxopropan-2-yl)carbamate (Example 229A)**

(R)-2-((tert-butoxycarbonyl)amino)-3-(3,5-difluoro-4-hydroxyphenyl)propanoic acid (500 mg, 1.58 mmol) and cyclohexanamine (172 mg, 1.74 mmol), DIPEA (822 μ L, 4.74 mmol) and HATU (719 mg, 1.90 mmol) were stirred at RT in a mixture of DMF (2 mL) and DCM (10 mL). After 3 h the reaction mixture was concentrated in vacuo and the
 10 residue was partitioned between DCM (20 mL) and saturated sodium bicarbonate solution (15 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on a Si cartridge (40 g) eluting with 0-100% ethyl acetate in cyclohexane to give a cream foam (468 mg).

LCMS (Method 6): R_t = 1.40 min, m/z 397.1 $[\text{M}-\text{H}]^-$

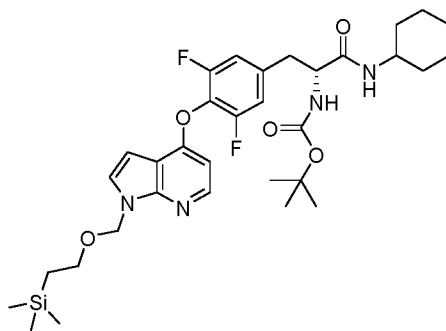
15 **Step B**



tert-Butyl (R)-3-(4-((6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3,5-difluorophenyl)-1-(cyclohexylamino)-1-
oxopropan-2-yl)carbamate (Example 229B)

20 Intermediate 229B was prepared from Intermediate 229A and Intermediate 227B using a procedure similar to that used for Intermediate 227C.

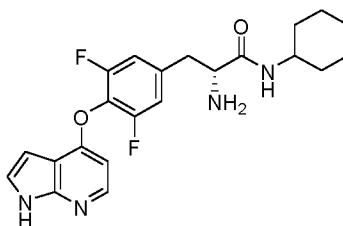
LCMS (Method 6): R_t = 1.97 min, m/z 679.3 $[\text{M}+\text{H}]^+$

Step C

tert-Butyl (R)-1-(cyclohexylamino)-3-(3,5-difluoro-4-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxopropan-2-yl carbamate (Example 229C)

Intermediate 229C was prepared from Intermediate 229B using a method analogous to that used for Intermediate 227D.

LCMS (Method 6): $R_t = 1.87$ min, m/z 645.4 $[M+H]^+$

Step D

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3,5-difluorophenyl)-2-amino-N-cyclohexylpropanamide (Example 229)

Intermediate 229C (216 mg, 0.336 mmol) was dissolved in DCM (5 mL) and TFA (1 mL) was added. After stirring at RT for 1 h the volatiles were evaporated and the residue was dissolved in methanol (10 mL). 2M lithium hydroxide (2 mL) was added and the reaction was stirred at RT for 18 h. The methanol was evaporated and the aqueous mixture was extracted with DCM (12 mL). The organic was dried (Na_2SO_4) and evaporated. The product was purified by HPLC eluting with a gradient of 10-98% acetonitrile in water (0.1% formic acid added) to give a white solid (67 mg).

LCMS (Method 1): $R_t = 2.86$ min, m/z 415.2 $[M+H]^+$

^1H NMR (400 MHz, DMSO) δ 11.85 (s, 1H), 8.07 (d, $J=5.4$ Hz, 1H), 7.71 (d, $J=8.0$

Hz, 1H), 7.41 (dd, J=2.5, 3.4 Hz, 1H), 7.18 (d, J=9.0 Hz, 2H), 6.36 (d, J=5.5 Hz, 1H), 6.34 (dd, J=1.9, 3.4 Hz, 1H), 3.58-3.49 (m, 1H), 3.47 (t, J=6.7 Hz, 1H), 2.91 (dd, J=6.1, 13.2 Hz, 1H), 2.77 (dd, J=7.5, 13.3 Hz, 1H), 1.73-1.49 (m, 6H), 1.32-1.03 (m, 6H).

The following racemic examples were resolved using the conditions given below to
5 give the pure enantiomers.

Racemate	Separation	Analysis	1st eluting	2nd eluting
Example 8 Separation 1	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 100 mL/min 40°C 230 nM; column dimensions 250 x 20 mm id 5µm	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 0.95 mL/min 40°C; column dimensions 150 x 2 mm, 5µm	Rt = 5.6 min (further purification required)	Rt = 6.4 min (further purification required)
Example 8 Separation 2 First eluting diastereoisomer A	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 100 mL/min 40°C 220 nM; column dimensions 250 x 20 mm id 5µm	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 0.95 mL/min 40°C; column dimensions 150 x 2 mm, 5µm	Example 8A Rt = 5.6 mins	
Example 8 Separation 2 Second eluting diastereoisomer B	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 100 mL/min 40°C 220 nM; column dimensions 250 x 20 mm id 5µm	MD SFC YMC Amylose-C 30/70 MeOH/MeCN (50/50/0.1% DEA)/CO ₂ 0.95 mL/min 40°C; column dimensions 150 x 2 mm, 5µm		Example 8B Rt = 6.3 mins
Example 132	MD SFC YMC Amylose-C 40/60 IPA(0.1% DEA)/CO ₂ 100 mL/min 40°C 225 nM; column dimensions 250 x 20 mm id 5µm	MD SFC YMC Amylose-C 30/70 IPA(0.1% DEA)/CO ₂ 5 mL/min 40°C 225 nM; column dimensions 250 x 4.6 mm 5µm	Example 132A Rt = 3.1 min	Example 132B Rt = 3.9 min

Racemate	Separation	Analysis	1st eluting	2nd eluting
Example 91	MD SFC YMC Amylose-C 40/60 IPA(0.1% DEA)/CO ₂ 70 mL/min 40°C 250 nM; column dimensions 250 x 20 mm id 5µm	MD SFC YMC Amylose-C 40/60 IPA(0.1% DEA)/CO ₂ 5 mL/min 40°C 250 nM; column dimensions 250 x 4.6 mm 5µm	Example 91A Rt = 2.1 min	Example 91B Rt = 3.2 min
Example 57	MD SFC YMC Amylose-C 30/70 MeOH (0.1% DEA)/CO ₂ 100 mL/min 40°C 220 nM; column dimensions 250 x 20mm id 5µm	MD SFC YMC Amylose-C 30/70 MeOH (0.1% DEA)/CO ₂ 5.0 mL/min 40°C 220 nM; column dimensions 250 x 4.6 mm 5µm	Example 57A Rt = 5.0 min	Example 57B Rt = 6.1 min
Example 55	Chiral HPLC (Method A)	Diacel Chiralpak IA, Solvent A CO ₂ Solvent B IPA (+ 0.1% DEA) 1.7 mL/min Time %A %B 0 95 5 0.5 95 5 2 45 55 4.5 45 55 4.6 95 5 5 95 5 40°C 400 nM; column dimensions 100 x 3.0 mm 3µm	Example 54 Rt = 3.16 min	Example 55 Rt = 3.22 min

PHARMACOLOGICAL ACTIVITY OF THE COMPOUNDS OF THE INVENTION.

In vitro inhibitory activity assay description

The effectiveness of compounds of the present invention to inhibit Rho kinase activity can be determined in a 10µl assay containing 40mM Tris pH7.5, 20mM MgCl₂ 0.1mg/ml BSA, 50µM DTT and 2.5µM peptide substrate (Myelin Basic Protein) using an ADP-Glo kit (Promega). Compounds were dissolved in DMSO such that the final concentration of DMSO was 1% in the assay. All reactions/incubations are performed at 25°C. Compound (2ul) and either Rho kinase 1 or 2 (4µl) were mixed and incubated for 30

mins. Reactions were initiated by addition of ATP (4μl) such that the final concentration of ATP in the assay was 10μM. After a 1 hour incubation 10μl of ADP-Glo Reagent was added and after a further 45 minute incubation 20ul of Kinase Detection Buffer was added and the mixture incubated for a further 30 minutes. The luminescent signal was measured on a luminometer. Controls consisted of assay wells that did not contain compound with background determined using assay wells with no enzyme added. Compounds were tested in dose-response format and the inhibition of kinase activity was calculated at each concentration of compound. To determine the IC₅₀ (concentration of compound required to inhibit 50% of the enzyme activity) data were fit to a plot of % inhibition vs Log₁₀ compound concentration using a sigmoidal fit with a variable slope and fixing the maximum to 100% and the minimum to 0%. To determine the Ki values the Cheng-Prusoff equation was utilized ($K_i = IC_{50} / (1 + [S] / K_m)$).

Compounds according to the invention showed Ki values lower than 5 μM and for most of the compounds of the invention Ki is even lower than 500 nM.

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

Table 1

Example	Activity ROCK 1	Activity ROCK 2
1	+++	+++
2	+++	+++
3	++	++
4	+++	+++
5	+++	+++
6	+++	+++
7	+++	+++
8	+++	+++
9	+++	+++
10	+++	+++
11	+++	+++
12	+++	+++
13	+++	+++
14	+++	+++
15	+++	+++
16	+++	+++

Example	Activity ROCK 1	Activity ROCK 2
17	+++	+++
18	+++	+++
19	+++	+++
20	+++	+++
21	+++	+++
22	+++	+++
23	+++	+++
24	+++	+++
25	+++	+++
26	+++	+++
27	+++	+++
28	+++	+++
29	+++	+++
30	+++	+++
31	+++	+++
32	+++	+++

Example	Activity ROCK 1	Activity ROCK 2
33	+++	+++
34	+++	+++
35	+++	+++
36	+++	+++
37	+++	+++
38	+++	+++
39	++	++
40	++	+++
41	+++	+++
42	+++	+++
43	+++	+++
44	++	+++
45	+++	+++
46	+++	+++
47	+++	+++
48	+++	+++
49	+++	+++
50	+++	+++
51	+++	+++
52	+++	+++
53	+++	+++
54	+++	+++
55	++	++
56	+++	+++
57	+++	+++
58	+++	+++
59	+++	+++
60	+++	+++
61	+++	+++
62	+++	+++
63	+++	+++
64	++	+++
65	+++	+++
66	+++	+++
67	+++	+++
68	+++	+++
69	+++	+++
70	+++	+++
71	+++	+++
72	+++	+++
73	+++	+++
74	+++	+++
75	+++	+++

Example	Activity ROCK 1	Activity ROCK 2
76	+++	+++
77	+++	+++
78	+++	+++
79	+++	+++
80	+++	+++
81	+++	+++
82	+++	+++
83	+++	+++
84	++	++
85	++	++
86	+	+
87	+++	+++
88	+++	+++
89	+++	+++
90	+++	+++
91	++	+++
92	++	++
93	++	++
94	+++	+++
95	+	+
96	+	+
97	++	++
98	+	+
99	++	++
100	+	+
101	++	++
102	+	+
103	++	++
104	+	+
105	++	++
106	+	+
107	+++	+++
108	++	++
109	++	++
110	+	++
111	++	+++
112	+	++
113	+	++
114	+++	+++
115	+++	+++
116	++	++
117	++	++
118	++	++

Example	Activity ROCK 1	Activity ROCK 2
119	+++	+++
120	++	+++
121	++	++
122	++	+++
123	+++	+++
124	+++	+++
125	++	++
126	++	++
127	+++	+++
128	+++	+++
129	+++	+++
130	+++	+++
131	++	+++
132	+++	+++
133	+++	+++
134	+++	+++
135	+++	+++
136	++	++
137	+++	+++
138	++	++
139	+++	+++
140	++	++
141	+++	+++
142	++	++
143	+	+
144	+	+
145	+++	+++
146	+++	+++
147	++	+++
148	+++	+++
149	+++	+++
150	++	++
151	+	+
152	+++	+++
153	+++	+++
154	+++	+++
155	+++	+++
156	+++	+++
157	+++	+++
158	+++	+++
159	+++	+++
160	+++	+++
161	+++	+++

Example	Activity ROCK 1	Activity ROCK 2
162	+++	+++
163	+++	+++
164	+++	+++
165	+++	+++
166	+++	+++
167	+++	+++
168	+++	+++
169	+++	+++
170	+++	+++
171	++	++
172	+++	+++
173	+++	+++
174	+++	+++
175	+++	+++
176	++	+++
177	+++	+++
178	+	+
179	++	++
180	++	++
181	+	+
182	+	+
183	+	++
184	+++	+++
185	+	+
186	+++	+++
187	+++	+++
188	+++	+++
189	+++	+++
190	+++	+++
191	+++	+++
192	+++	+++
193	++	++
194	+++	+++
195	+++	+++
196	+++	+++
197	+++	+++
198	+++	+++
199	+++	+++
200	+++	+++
201	+++	+++
202	++	++
203	+++	+++
204	+++	+++

Example	Activity ROCK 1	Activity ROCK 2
205	+++	+++
206	+++	+++
207	+++	+++
208	+++	+++
209	++	+++
210	++	++
211	++	++
212	++	++
213	+++	+++
214	++	++
215	++	++
216	+++	+++
217	+++	+++
218	+++	+++
219	+++	+++
220	+++	+++
221	+++	+++

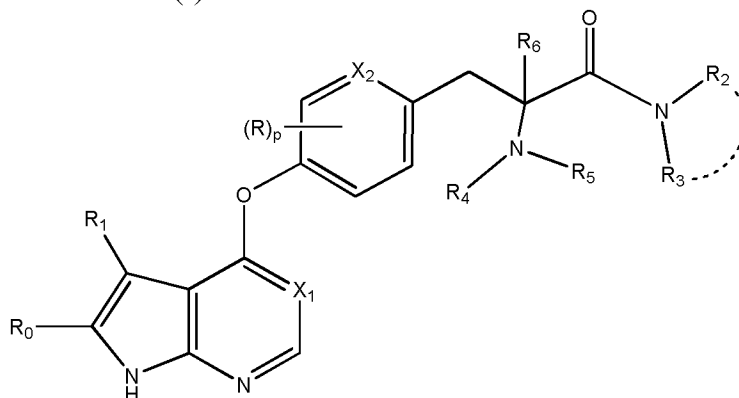
Example	Activity ROCK 1	Activity ROCK 2
222	+++	+++
223	+++	+++
224	+++	+++
225	+	+
226	++	++
227	+	+
228	+	++
229	++	++
132A	+++	+++
132B	++	+++
8A	+++	+++
8B	+++	+++
91A	+++	+++
91B	++	++
57A	++	+++
57B	+++	+++

wherein the compounds are classified in term of potency with respect to their inhibitory activity on ROCK-I and ROCK-II isoforms according to the following classification criterion:

- 5 + + + : $K_i < 3 \text{ nM}$
 + + : K_i in the range 3-30 nM
 + : $K_i > 30 \text{ nM}$

CLAIMS

1. A compound of formula (I)



(I)

5 wherein

X_1 , and X_2 are in each occurrence independently a CH group or a nitrogen atom.

p is zero or an integer from 1 to 3

each R , when present, is an halogen;

R_0 and R_1 are independently selected from the group consisting of

10 -H,

halogen,

- NR_7R_8 ,

-CN,

(C_1 - C_6) alkyl,

15 (C_1 - C_6) haloalkyl,

(C_1 - C_6) hydroxyalkyl,

(C_1 - C_6) aminoalkyl,

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

(C_3 - C_{10}) cycloalkyl,

20 (C_2 - C_6) alkenyl,

(C_5 - C_7) cycloalkenyl,

(C₂-C₆) alkynyl,
(C₂-C₆) hydroxyalkynyl,
aryl, heteroaryl and (C₃-C₆) heterocycloalkyl
each of which aryl, heteroaryl and (C₃-C₆) heterocycloalkyl

5 being in his turn optionally and independently substituted with one or more groups
selected from

halogen,

-OH,

-CN,

10 -NR₇R₈,

-CH₂NR₇R₈,

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

(C₁-C₆) hydroxyalkyl,

15 (C₂-C₆) alkenyl,

(C₂-C₆) alkynyl,

(C₂-C₆) hydroxyalkynyl;

R₂ and R₃, the same or different, are selected from the group consisting of

-H,

20 (C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

(C₁-C₆) hydroxyalkyl,

(C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy (C₁-C₆) alkyl,

25 (C₃-C₁₀)cycloalkyl,

(C₃-C₈)heterocycloalkyl,

aryl,

heteroaryl,

aryl(C₁-C₆)alkyl,
heteroaryl(C₁-C₆)alkyl,
(C₃-C₈)cycloalkyl(C₁-C₆)alkyl,
(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl,

5 each of said aryl, heteroaryl, cycloalkyl, heterocycloalkyl is further optionally substituted by one or more group selected independently from halogen, -CN, -OH, (C₁-C₈)alkyl, (C₁-C₆) haloalkyl, (C₁-C₁₀)alkoxy, aryl, aryl(C₁-C₆)alkyl, carbamoyl, (C₁-C₆) aminoalkyl, (C₁-C₆) hydroxyalkyl; or

R₂ and R₃, in the alternative, taken together with the nitrogen atom they are linked
10 to, to form a mono- or bi-cyclic saturated or partially saturated heterocyclic radical, preferably a 4 to 6 membered monocyclic radical, at least one further ring carbon atom in the said heterocyclic radical is optionally replaced by at least one further heteroatom independently selected from N, S or O and/or may bear an -oxo (=O) substituent group, said heterocyclic radical is further optionally including spiro disubstitution as well as
15 substitution on two adjacent or vicinal atoms forming an additional 5 to 6 membered cyclic or heterocyclic, saturated, partially saturated or aromatic, ring;

said heterocyclic radical being optionally in its turn further substituted with one or more groups selected from the group consisting of

halogen,
20 hydroxyl,
-NR₇R₈,
-CH₂NR₇R₈,
(C₁-C₆) alkyl,
(C₁-C₆) haloalkyl,
25 (C₁-C₆) hydroxyalkyl,
(C₂-C₆) alkenyl,
(C₂-C₆) alkynyl,
(C₂-C₆) hydroxyalkynyl,

- (C₁-C₆) alkoxy (C₁-C₆) alkyl,
 (C₁-C₆) alkanoyl,
 carbamoyl,
 (C₃-C₆) cycloalkyl-carbonyl,
 5 (C₃-C₆) heterocycloalkyl-carbonyl,
 aryl(C₁-C₆)alkyl,
 aryl alkanoyl,
 arylsulfonyl,
 heteroaryl(C₁-C₆)alkyl,
 10 heteroaryl-carbonyl,
 heteroaryloxy,
 (C₃-C₆) cycloalkyl,
 (C₃-C₈)cycloalkyl(C₁-C₆)alkyl
 (C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl,
 15 aryl and heteroaryl
- each of said cycloalkyl, aryl and heteroaryl being further optionally substituted by
 halogen, (C₁-C₈)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₆)alkylthio, (C₁-C₆) aminoalkyl, (C₁-C₆)
 aminoalkoxyl, carbamoyl, (C₁-C₆)alkyl-sulfonyl;
- R₄ and R₅ are in each occurrence independently selected in the group consisting of
 20 H,
 (C₁-C₆) alkyl,
 (C₁-C₆) haloalkyl,
 (C₁-C₆) hydroxyalkyl,
 (C₁-C₆) aminoalkyl,
 25 (C₁-C₆) alkoxyl,
 (C₁-C₆) alkoxy-(C₁-C₆) alkyl,
 (C₃-C₆) cycloalkyl-(C₁-C₆) alkyl,
 (C₃-C₆) heterocycloalkyl-(C₁-C₆) alkyl,

(C₃-C₆) cycloalkyl-carbonyl,

(C₃-C₆) heterocycloalkyl-carbonyl,

aryl, heteroaryl and (C₃-C₆) heterocycloalkyl;

wherein any of said (C₃-C₆) cycloalkyl, aryl, heteroaryl and (C₃-C₆)

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

halogen,

-OH,

(C₁-C₆) alkyl;

10 R₆ is selected from the group consisting of -H, (C₁-C₆) alkyl, (C₁-C₆) haloalkyl;

R₇ and R₈ are in each occurrence independently selected in the group

H,

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

15 (C₁-C₆) hydroxyalkyl,

(C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy,

(C₁-C₆) alkoxy-(C₁-C₆) alkyl,

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

20 aryl, heteroaryl and (C₃-C₆) heterocycloalkyl;

wherein any of said aryl, heteroaryl and (C₃-C₆) heterocycloalkyl in its turn is optionally and independently substituted with one or more groups selected from

halogen,

-OH,

25 (C₁-C₆) alkyl; or

R₇ and R₈ are taken together with the nitrogen atom they are linked to, to form a 4 to 6 membered heterocyclic radical, wherein at least one further ring carbon atom in the said heterocyclic radical may be replaced by at least one group selected from N, S or O;

said heterocyclic radical can be further optionally substituted by a group selected from

H,

-CN,

halogen,

5 -oxo,

-NR₇R₈

(C₁-C₆) alkyl,

(C₁-C₆) haloalkyl,

(C₁-C₆) hydroxyalkyl,

10 (C₁-C₆) aminoalkyl,

(C₁-C₆) alkoxy,

(C₁-C₆) alkoxy-(C₁-C₆) alkyl,

alkanoyl;

or pharmaceutically acceptable salts and solvates thereof.

15 2. A compound according to Claim 1 wherein each of X₁ and X₂ is a CH group, all the other variables being as defined in claim 1;

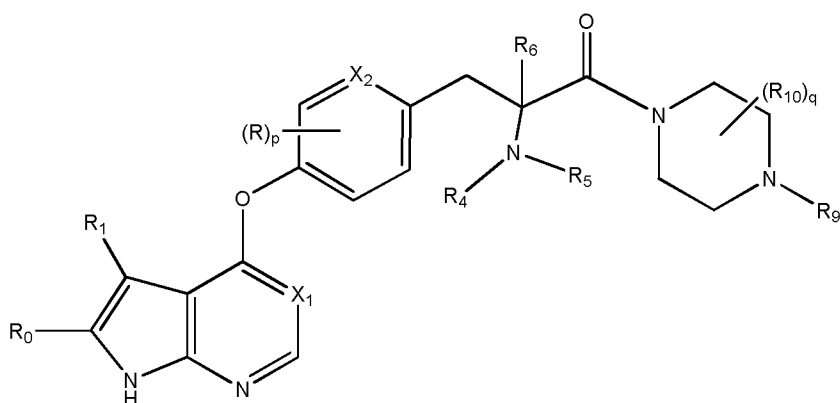
or pharmaceutically acceptable salt and solvates thereof.

3. A compound according to Claim 1

wherein R₂ and R₃, are taken together with the nitrogen atom they are linked to, to

20 form a mono-cyclic saturated heterocyclic radical, which is a piperazine ring;

represented by the formula Ib:



wherein R₉ is selected from the group consisting of

(C₁-C₆) alkyl,

(C₁-C₆) alkoxy (C₁-C₆) alkyl,

(C₁-C₆) alkanoyl,

5 carbamoyl,

(C₃-C₆) cycloalkyl-carbonyl,

(C₃-C₆) heterocycloalkyl-carbonyl,

aryl(C₁-C₆)alkyl,

aryl alkanoyl,

10 arylsulfonyl,

heteroaryl(C₁-C₆)alkyl,

heteroaryl-carbonyl,

heteroaryloxy,

(C₃-C₆) cycloalkyl,

15 (C₃-C₈)cycloalkyl(C₁-C₆)alkyl,

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

aryl and heteroaryl

each of said cycloalkyl, heterocycloalkyl, aryl and heteroaryl being further optionally substituted by one or more halogen, (C₁-C₈)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₆)alkylthio, (C₁-C₆) aminoalkyl, (C₁-C₆) aminoalkoxyl, carbamoyl, (C₁-C₆)alkyl-sulfonyl;

20 and wherein said piperazine ring is further optionally substituted by one or more substituent group R₁₀ selected in the group consisting of (C₁-C₆) alkyl, (C₁-C₆) hydroxyalkyl, and aryl;

all the other variables being as defined in claim 1,

25 or pharmaceutically acceptable salt and solvates thereof.

4. A compound according to claim 1 wherein

X₁, and X₂ are both a CH group;

p is zero or an integer from 1 to 3;

each R, when present, is a halogen;

R₀ is -H, and

R₁ is independently selected from the group consisting of

-CN,

5 (C₁-C₆) alkyl,

(C₁-C₆) hydroxyalkyl,

R₂ is -H,

and R₃ is selected from the group consisting of

(C₃-C₁₀)cycloalkyl,

10 (C₃-C₈)heterocycloalkyl,

heteroaryl(C₁-C₆)alkyl;

each of said heteroaryl, cycloalkyl, heterocycloalkyl is further optionally substituted
by one or more (C₁-C₈)alkyl or (C₁-C₆) hydroxyalkyl;

R₄ and R₅ are both H,

15 R₆ is -H;

or pharmaceutically acceptable salt and solvate thereof.

5. A compound according to claim 1 wherein

X₁, and X₂ are in each occurrence independently a CH group or a nitrogen atom,

p is zero or an integer from 1 to 3;

20 each R, when present, is fluoro;

R₀ is -H or (C₁-C₆) alkyl which is methyl, and R₁ is independently selected from
the group consisting of

-H,

Halogen which is Bromo, Chloro, Iodo, Fluoro,

25 -NR₇R₈,

-CN,

(C₁-C₆) alkyl which is methyl,

(C₁-C₆) haloalkyl,

- (C₁-C₆) hydroxyalkyl which is hydroxymethyl, hydroxyethyl,
 (C₁-C₆) aminoalkyl,
 (C₁-C₆) alkoxy-(C₁-C₆) alkyl which is methoxymethyl,
 (C₃-C₁₀) cycloalkyl which is cyclopropyl,
 5 (C₂-C₆) alkenyl,
 (C₅-C₇) cycloalkenyl,
 (C₂-C₆) alkynyl,
 (C₂-C₆) hydroxyalkynyl which is hydroxypropynyl,
 aryl which is phenyl, hydroxyphenyl,
 10 heteroaryl which is isoxazolyl, N-methylimidazolyl, pyridinyl, thiazolyl, N-ethyl
 pyrazolyl, thiophenyl-carbonitrile, and
 (C₃-C₆) heterocycloalkyl which is dihydropyrrolyl, dihydrofuranyl,
 R₂ is -H or (C₁-C₆) alkyl which is methyl and R₃, is independently selected from the
 group consisting of
 15 (C₁-C₆) alkyl which is methyl,
 (C₁-C₆) haloalkyl,
 (C₁-C₆) hydroxyalkyl,
 (C₁-C₆) aminoalkyl which is dimethylaminoethyl, dimethylaminopropyl,
 (C₁-C₆) alkoxy (C₁-C₆) alkyl which is methoxypropyl,
 20 (C₃-C₁₀)cycloalkyl which is cyclohexyl, hydroxymethylcyclohexyl,
 hydroxyethylcyclohexyl, cyano-cyclohexyl, 4-aminocarbonyl-cyclohexane-4-yl, 4-
 dimethylaminomethyl-cyclohexane-4-yl,
 (C₃-C₈)heterocycloalkyl which is N-methylpiperidinyl, (hydroxymethyl)-N-
 methylpiperidinyl, N-benzylpiperidinyl, N-methylazetidin-3-yl, tetrahydropyranyl, 4-
 25 hydroxymethyl-tetrahydropyran-4-yl, quinuclidinyl,
 aryl which is phenyl, trifluoromethylphenyl, dihydroindenyl,
 heteroaryl which is thiazolyl, pyridinyl, chloropyridinyl, isoquinolinyl,
 aryl(C₁-C₆)alkyl which is benzyl, o-, m-, p-hydroxymethylbenzyl, phenethyl,

heteroaryl(C₁-C₆)alkyl which is (pyridinyl)ethyl, (thiophene-yl)methyl, (N-phenyl-pyrazolyl)ethyl,

(C₃-C₈)cycloalkyl(C₁-C₆)alkyl which is cyclohexylmethyl,

(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkyl which is (piperidin-4-yl)methyl, (N-benzylpiperidinyl)methyl, (N-methylpiperidin-4-yl)methyl, N-methylazetidin-3-yl-methyl, morpholinopropyl; or

R₂ and R₃, in the alternative, taken together with the nitrogen atom they are linked to, to form a mono-cyclic group which is piperazin-N-yl, methylpiperazin-N-yl, phenyl-N-methylpiperazin-N-yl, N-phenyl-piperazin-N-yl, trimethylpiperazin-N-yl, 4-benzyl-3,5-dimethylpiperazin-N-yl, (hydroxymethyl)-N-methylpiperazin-N-yl, acetyl(piperazin-N-yl), phenylacetyl(piperazin-N-yl), benzoyl(piperazin-N-yl), 4-(((dimethylamino)methyl)benzoyl)piperazin-1-yl, cyclopropyl(piperazin-N-yl), cyclopropylmethyl(piperazin-N-yl), cyclopropanecarbonyl(piperazin-N-yl), cyclohexanecarbonyl(piperazin-N-yl), N-methylpiperidine-4-carbonyl(piperazin-N-yl), 4-(pyridine-3-carbonyl)piperazin-N-yl, 4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-N-yl, 4-(1-methyl-1H-imidazole-4-carbonyl)piperazin-N-yl, 4-(1H-thiazole-4-carbonyl)piperazin-N-yl, 4-dimethylaminocarbonyl(piperazin-N-yl), (phenylsulfonyl)piperazin-N-yl, (pyridinyl)piperazin-N-yl, (pyridinylmethyl)piperazin-N-yl, (methoxyethyl)piperazin-N-yl, (benzyl)piperazin-N-yl, (methoxybenzyl)piperazin-N-yl, (3-(dimethylaminopropoxy)benzyl)piperazin-N-yl, (fluorobenzyl)piperazin-N-yl, (methylbenzyl)piperazin-N-yl, N-(((methylaminocarbonyl)phenyl)methyl)piperazine-N-yl, N-(((methylaminocarbonyl)furanyl)methyl)piperazine-N-yl, (phenethyl)piperazin-N-yl, (pyrimidinylmethyl)piperazin-N-yl, (2(methylthio)pyrimidinylmethyl)piperazin-N-yl, (((methylsulfonyl)piperidin-4-yl)methyl)piperazin-N-yl, ((N-methyl-imidazol-5-yl)methyl)piperazin-N-yl, ((1-methyl-1H-imidazol-2-yl)methyl)piperazin-N-yl, ((methylthiazolyl)methyl)piperazin-N-yl, ((pyrazin-2-yl)methyl)piperazin-N-yl, ((1-methyl-1H-pyrazol-4-yl)methyl)piperazin-N-yl, benzo[d][1,3]dioxol-5-ylmethyl)piperazin-N-yl, (quinoxalin-2-ylmethyl)piperazin-N-yl, ((1,2,3-thiadiazol-4-

yl)methyl)piperazin-N-yl, (pyridazin-4-ylmethyl)piperazin-N-yl,

pyrrolidin-N-yl, phenylpyrrolidin-N-yl, (pyridinyl)pyrrolidin-N-yl,

piperidin-N-yl, (dimethylamino)piperidin-N-yl, 4-

((dimethylamino)methyl)piperidin-N-yl, benzylpiperidin-N-yl, benzylhydroxypiperidin-

5 N-yl, pyridinylpiperidin-N-yl, pyridinyloxypiperidin-N-yl, (phenylsulfonyl)piperidin-N-yl,

4-phenyl-5,6-dihydropyridin-1(2H)-yl,

phenylmorpholin-N-yl,

3-(dimethylamino)azetidin-N-yl, 3-(dimethylamino)methyl-azetidin-N-yl,

10 3-(dimethylamino)pyrrolidin-N-yl, 3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-N-yl,

3-(dimethylamino)piperidin-N-yl,

or a bi-cyclic group which is 5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl, 3,4-dihydro-2,7-naphthyridin-2(1H)-yl, 1H-pyrrolo[3,4-c]pyridin-2(3H)-yl,

15 hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl, 3,4-dihydroisoquinolin-2(1H)-yl, 5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl, 2,6-diazaspiro[3.3]heptan-2-yl, 6-methyl-2,6-diazaspiro[3.3]heptan-2-yl, 7-methyl-2,7-diazaspiro[3.5]nonan-2-yl, 2-methyl-2,9-diazaspiro[5.5]undecan-9-yl, 9-methyl-3,9-diazaspiro[5.5]undecan-3-yl,

20 octahydropyrrolo[3,4-c]pyrrol-2-yl or 5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl;

R₄ is selected in the group consisting of H, (C₁-C₆) alkyl which is methyl, (C₃-C₆) cycloalkyl-(C₁-C₆) which is cyclohexylmethyl, and (C₃-C₆) cycloalkyl-carbonyl which is cyclohexylcarbonyl or (pyrrolidin-3-yl)carbonyl;

and R₅ is independently selected in the group consisting of H, (C₁-C₆) alkyl which
25 is methyl;

R₆ is selected from the group consisting of -H and (C₁-C₆) alkyl which is methyl;

or pharmaceutically acceptable salts and solvates thereof.

6. A compound according to claim 1 wherein selected from:

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide;

(S)-2-amino-1-(7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one;

(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylmorpholino)propan-1-one;

10 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenylpiperazin-1-yl)propan-1-one;

(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methyl-3-phenylpiperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one;

15 (2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one;

(S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

20 (S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yloxy)piperidin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one;

25 (S)-2-amino-1-(4-benzylpiperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-(dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(2S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(hexahydropyrazino[2,1-c][1,4]oxazin-8(1H)-yl)propan-1-one;

5 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3,3,4-trimethylpiperazin-1-yl)propan-1-one;

10 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-methoxyethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenyl-5,6-dihydropyridin-1(2H)-yl)propan-1-one;

15 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperazin-1-yl)propan-1-one;

(S)-4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)-N,N-dimethylpiperazine-1-carboxamide;

20 (S)-2-amino-1-((1S,4S)-5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one;

(S)-2-amino-1-((3S,5R)-4-benzyl-3,5-dimethylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

25 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2,6-diazaspiro[3.3]heptan-2-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one;

5 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((3aR,6aS)-hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(hydroxymethyl)cyclohexyl)propanamide;

10 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-N-(1-cyanocyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-1-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamido)cyclohexanecarboxamide;

15 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-(2-hydroxyethyl)cyclohexyl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)-1-methylpiperidin-4-yl)propanamide;

20 (S)-2-amino-N-(1-((dimethylamino)methyl)cyclohexyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-N-((1-methylpiperidin-4-yl)methyl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylpiperidin-4-yl)methyl)propanamide;

25 (S)-2-amino-1-(3-(dimethylamino)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylazetidin-3-yl)propanamide;

(S)-2-amino-1-((R)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-methyl-N-(1-methylpiperidin-4-yl)propanamide;

5 (S)-2-amino-1-(4-((dimethylamino)methyl)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((R)-quinuclidin-3-yl)propanamide;

10 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-((1-methylazetidin-3-yl)methyl)propanamide;

(S)-2-amino-1-(3-((dimethylamino)methyl)azetidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-((S)-3-(dimethylamino)pyrrolidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

15 (S)-2-amino-1-((R)-3-(dimethylamino)piperidin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-ylmethyl)piperazin-1-yl)propan-1-one;

20 2-amino-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-phenethylpiperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

25 (R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(1-phenyl-1H-pyrazol-4-yl)ethyl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

2-amino-1-(4-(cyclopropylmethyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one;

2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

10 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(thiophen-2-ylmethyl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(4-(hydroxymethyl)benzyl)propanamide;

2-amino-N-(2,3-dihydro-1H-inden-2-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

15 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-(hydroxymethyl)-4-methylpiperazin-1-yl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(1H-pyrrolo[3,4-c]pyridin-2(3H)-yl)propan-1-one;

20 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(pyridin-4-yl)pyrrolidin-1-yl)propan-1-one;

2-amino-1-(3,4-dihydro-2,7-naphthyridin-2(1H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-methoxypropyl)propanamide;

25 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-2-yl)ethyl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-3-yl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(pyridin-4-yl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methylbenzyl)piperazin-1-yl)propan-1-one;

5 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(3-methylbenzyl)piperazin-1-yl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-fluorobenzyl)piperazin-1-yl)propan-1-one;

10 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(4-methoxybenzyl)piperazin-1-yl)propan-1-one;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenethylpropanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperidin-1-yl)propan-1-one;

15 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(isoquinolin-5-yl)propanamide;

2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(3-morpholinopropyl)propanamide;

20 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-yl)piperazin-1-yl)propan-1-one;

2-amino-1-(5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

2-amino-N-((1-benzylpiperidin-4-yl)methyl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

25 2-amino-N-(1-benzylpiperidin-4-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

First eluting rac-diastereoisomer 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one;

Second eluting rac-diastereoisomer 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(2-phenylpyrrolidin-1-yl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 (S)-2-amino-N-(3-methoxypropyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

10 (S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide;

15 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-N-methylpropanamide;

20 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(6-chloropyridin-3-yl)propanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(2-(dimethylamino)ethyl)propanamide;

25 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzylpropanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(tetrahydro-2H-pyran-4-yl)propanamide;

5 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-N-methylpropanamide;

10 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(1-methylpiperidin-4-yl)propanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide;

15 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(thiazol-2-yl)propanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide;

20 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)propanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-phenylpropanamide;

25 (S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide;

3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N,N-dimethylpropanamide;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propanamide;

10 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one;

(S)-2-amino-1-(4-cyclopropylpiperazin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one;

15 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one;

2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one;

20 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-4-yl)piperidin-1-yl)propan-1-one;

(S)-2-amino-1-(4-benzyl-4-hydroxypiperidin-1-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)propan-1-one;

25 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(pyridin-3-yloxy)piperidin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-(4-(phenylsulfonyl)piperidin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

5 (S)-2-amino-3-(3-fluoro-4-((5-methyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-1-((3S,5R)-3,4,5-trimethylpiperazin-1-yl)propan-1-one;

(S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-
10 (methylamino)propanamide;

2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

1-(4-acetylpiperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

15 (S)-2-amino-N-cyclohexyl-N-methyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(R)-2-amino-N-benzyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide;

(R)-2-amino-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide;

25 (S)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(R)-2-amino-N-(cyclohexylmethyl)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(R)-2-amino-N-cyclohexyl-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

5 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(cyclohexylmethyl)-N-methylpropanamide;

(R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-benzyl-N-methylpropanamide;

10 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-cyclohexylpropanamide;

(S)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-2-amino-N-phenylpropanamide;

15 (R)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(R)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-phenylpropanamide;

20 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-cyclohexyl-2-methylpropanamide;

3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-2-methyl-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(piperazin-1-yl)propan-1-one;

25 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridazin-4-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-(methylthio)pyrimidin-4-yl)methyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyrazin-2-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)propan-1-one;

5 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((2-methylthiazol-4-yl)methyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)propan-1-one;

10 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(quinoxalin-2-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-1-(4-(4-(3-(dimethylamino)propoxy)benzyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-(methylsulfonyl)piperidin-4-yl)methyl)piperazin-1-yl)propan-1-one;

15 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyrimidin-5-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-((1-methyl-1H-pyrazol-4-yl)methyl)piperazin-1-yl)propan-1-one;

20 (S)-1-(4-((1,2,3-thiadiazol-4-yl)methyl)piperazin-1-yl)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-3-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)-N-methylbenzamide;

(S)-5-((4-(2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanoyl)piperazin-1-yl)methyl)-N-methylfuran-2-carboxamide;

25 (S)-2-amino-1-(4-benzoylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-(cyclohexanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(2-phenylacetyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-1-(4-(cyclopropanecarbonyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methylpiperidine-4-carbonyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-1-(4-(4-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

10 (S)-2-amino-1-(4-(3-((dimethylamino)methyl)benzoyl)piperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-nicotinoylpiperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-pyrazole-4-carbonyl)piperazin-1-yl)propan-1-one;

15 (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(1-methyl-1H-imidazole-4-carbonyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(thiazole-2-carbonyl)piperazin-1-yl)propan-1-one;

20 N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(dimethylamino)-1-oxopropan-2-yl)pyrrolidine-3-carboxamide;

N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-oxo-1-(phenylamino)propan-2-yl)pyrrolidine-3-carboxamide;

N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(cyclohexylamino)-1-oxopropan-2-yl)pyrrolidine-3-carboxamide;

25 N-(3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((2-(dimethylamino)ethyl)amino)-1-oxopropan-2-yl)cyclohexanecarboxamide;

3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-(dimethylamino)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexyl-2-(dimethylamino)propanamide;

(S)-N-cyclohexyl-2-(dimethylamino)-3-(4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

5 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-((cyclohexylmethyl)amino)-N-methylpropanamide;

(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide;

10 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)propan-1-one;

(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide;

(S)-2-amino-3-(4-((3-bromo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

15 (S)-2-amino-N-cyclohexyl-3-(4-((3-iodo-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

(S)-2-amino-3-(4-((3-chloro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide;

20 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-ethyl-1H-pyrazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(pyridin-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

25 (S)-5-(4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)phenoxy)-1H-pyrrolo[2,3-b]pyridin-3-yl)thiophene-2-carbonitrile;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(1-methyl-1H-imidazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(isoxazol-4-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

5 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

10 (S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydrofuran-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2,5-dihydro-1H-pyrrol-3-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-N-cyclohexyl-3-(4-((3-cyclopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

15 (S)-2-amino-3-(3-fluoro-4-((3-phenyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-(thiazol-5-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide;

20 (S)-2-amino-3-(4-((3-(4-hydroxyphenyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-N-cyclohexyl-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

25 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(1-methylpiperidin-4-yl)propanamide;

(S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)propan-1-one;

(S)-2-amino-N-(3-(dimethylamino)propyl)-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

5 (S)-2-amino-3-(3-fluoro-4-((3-(hydroxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propan-1-one;

(S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

10 (S)-2-amino-3-(3-fluoro-4-((3-(methoxymethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(4-methylpiperazin-1-yl)propan-1-one;

(S)-2-amino-1-(4-benzylpiperazin-1-yl)-3-(4-((3-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

(S)-2-amino-N-cyclohexyl-3-(4-((3-(3-hydroxyprop-1-yn-1-yl)-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propanamide;

15 (S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(tetrahydro-2H-pyran-4-yl)propanamide;

(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-cyclohexylpropanamide;

20 (S)-4-(4-(2-amino-3-(4-benzylpiperazin-1-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-cyclohexylpropanamide;

(S)-2-amino-3-(4-((3-cyano-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3-fluorophenyl)-N-(1-methylpiperidin-4-yl)propanamide;

25 4-(4-((S)-2-amino-3-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-oxopropyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

(S)-4-(4-(2-amino-3-oxo-3-(4-(pyridin-2-ylmethyl)piperazin-1-yl)propyl)-2-fluorophenoxy)-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile;

(S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-N-cyclohexylpropanamide;

(S)-3-(4-((7H-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one;

5 (S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-N-cyclohexylpropanamide;

(S)-3-(5-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)pyridin-2-yl)-2-amino-1-(4-benzylpiperazin-1-yl)propan-1-one;

10 (R)-3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)-3,5-difluorophenyl)-2-amino-N-cyclohexylpropanamide;

First eluting single enantiomer of 2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

Second eluting single enantiomer of 2-amino-1-(4-benzylpiperazin-1-yl)-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)propan-1-one;

15 First eluting diastereoisomer of (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one;

Second eluting diastereoisomer of (S)-2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-1-(3-(3-methyl-1,2,4-oxadiazol-5-yl)pyrrolidin-1-yl)propan-1-one;

20 First eluting enantiomer of 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide;

Second eluting enantiomer of 3-(4-((1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-2-amino-N-(4-(trifluoromethyl)phenyl)propanamide;

25 First eluting enantiomer of 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

Second eluting enantiomer of 2-amino-3-(3-fluoro-4-((3-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy)phenyl)-N-(2-(pyridin-4-yl)ethyl)propanamide;

or pharmaceutically acceptable salts and solvates thereof.

7. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, either alone or in combination with another one or more active ingredient, in admixture with one or more pharmaceutically acceptable carrier or excipient.
8. A pharmaceutical composition according to claim 7 suitable to be administered by inhalation, such as inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.
9. A compound according to any one of claims 1 to 6 for use as a medicament.
10. A compound according to any one of claims 1 to 6 for use in the prevention and /or treatment of pulmonary disease selected from the group consisting of asthma, chronic obstructive pulmonary disease COPD, idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH) and specifically Pulmonary Arterial Hypertension (PAH).
11. A combination of a compound as defined in any one of the claims 1 to 6 with one or more active ingredients selected from the classes consisting of organic nitrates and NO donors; inhaled NO; stimulator of soluble guanylate cyclase (sGC); prostacyclin analogue PGI₂ and agonist of prostacyclin receptors; compounds that inhibit the degradation of cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP); human neutrophilic elastase inhibitors; compounds inhibiting the signal transduction cascade; active substances for lowering blood pressure; neutral endopeptidase inhibitor; osmotic agents; ENaC blockers; anti-inflammatories including corticosteroids and antagonists of chemokine receptors; bronchodilators; antihistamine drugs; anti-tussive drugs; antibiotics and DNase drug substance and selective cleavage agents; agents that inhibit ALK5 and/or ALK4 phosphorylation of Smad2 and Smad3; tryptophan hydroxylase 1 (TPH1) inhibitors and multi-kinase inhibitors.
12. A device comprising the pharmaceutical composition according to claim 7, which may be a single- or multi-dose dry powder inhaler, a metered dose inhaler and a soft mist nebulizer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/052009

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61K31/519 C07D487/04 C07D519/00
A61P11/06

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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 2005/097790 A1 (BAYER HEALTHCARE AG [DE]; SCHIROK HARTMUT [DE]; RADTKE MARTIN [DE]; MI) 20 October 2005 (2005-10-20) claims; examples	1-12
A	WO 2006/009889 A1 (SMITHKLINE BEECHAM CORP [US]; SEHON CLARK A [US]; LEE DENNIS [US]; GOO) 26 January 2006 (2006-01-26) cited in the application claims; examples	1-12

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

1 March 2018

Date of mailing of the international search report

21/03/2018

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/052009

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	KAST ET AL.: "Cardiovascular effects of a novel potent and highly selective azaindole-based inhibitor of Rho-kinase", BRITISH JOURNAL OF PHARMACOLOGY, vol. 152, 15 October 2008 (2008-10-15), pages 1070-1080, XP002768087, the whole document -----	1-12

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Information on patent family members

International application No

PCT/EP2018/052009

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