

BIARYL KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to Provisional Patent Application USSN
5 62/061,591 filed October 8, 2014 and Provisional Patent Application USSN
61/973,942 filed April 2, 2014, hereby incorporated by reference in their entireties.

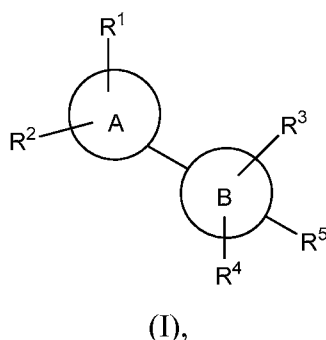
The present disclosure is generally directed to compounds which can inhibit
adaptor associated kinase 1 (AAK1), compositions comprising such compounds, and
methods for inhibiting AAK1.

10 Adaptor associated kinase 1 (AAK1) is a member of the Ark1/Prk1 family of
serine/threonine kinases. AAK1 mRNA exists in two splice forms termed short and
long. The long form predominates and is highly expressed in brain and heart
(Henderson and Conner, *Mol. Biol. Cell.* 2007, 18, 2698-2706). AAK1 is enriched
in synaptosomal preparations and is co-localized with endocytic structures in cultured
15 cells. AAK1 modulates clatherin coated endocytosis, a process that is important in
synaptic vesicle recycling and receptor-mediated endocytosis. AAK1 associates with
the AP2 complex, a hetero-tetramer which links receptor cargo to the clatherin coat.
The binding of clatherin to AAK1 stimulates AAK1 kinase activity (Conner et. al.,
Traffic 2003, 4, 885-890; Jackson et. al., *J. Cell. Biol.* 2003, 163, 231-236). AAK1
20 phosphorylates the mu-2 subunit of AP-2, which promotes the binding of mu-2 to
tyrosine containing sorting motifs on cargo receptors (Ricotta et. al., *J. Cell Bio.*
2002, 156, 791-795; Conner and Schmid, *J. Cell Bio.* 2002, 156, 921-929). Mu2
phosphorylation is not required for receptor uptake, but phosphorylation enhances the
efficiency of internalization (Motely et. al., *Mol. Biol. Cell.* 2006, 17, 5298-5308).
25 AAK1 has been identified as an inhibitor of Neuregulin-1/ErbB4 signaling in
PC12 cells. Loss of AAK1 expression through RNA interference mediated gene
silencing or treatment with the kinase inhibitor K252a (which inhibits AAK1 kinase
activity) results in the potentiation of Neuregulin-1 induced neurite outgrowth. These
treatments result in increased expression of ErbB4 and accumulation of ErbB4 in or
30 near the plasma membrane (Kuai et. al., *Chemistry and Biology* 2011, 18, 891-906).
NRG1 and ErbB4 are putative schizophrenia susceptibility genes (Buonanno, *Brain
Res. Bull.* 2010, 83, 122-131). SNPs in both genes have been associated with
multiple schizophrenia endophenotypes (Greenwood et. al., *Am. J. Psychiatry*

2011, 168, 930-946). Neuregulin 1 and ErbB4 KO mouse models have shown schizophrenia relevant morphological changes and behavioral phenotypes (Jaaro-Peled et. al., *Schizophrenia Bulletin* 2010, 36, 301-313; Wen et. al., *Proc. Natl. Acad. Sci. USA.* 2010, 107, 1211-1216). In addition, a single nucleotide polymorphism in an intron of the AAK1 gene has been associated with the age of onset of Parkinson's disease (Latourelle et. al., *BMC Med. Genet.* 2009, 10, 98). These results suggest that inhibition of AAK1 activity may have utility in the treatment of schizophrenia, cognitive deficits in schizophrenia, Parkinson's disease, neuropathic pain, bipolar disorder, and Alzheimer's disease.

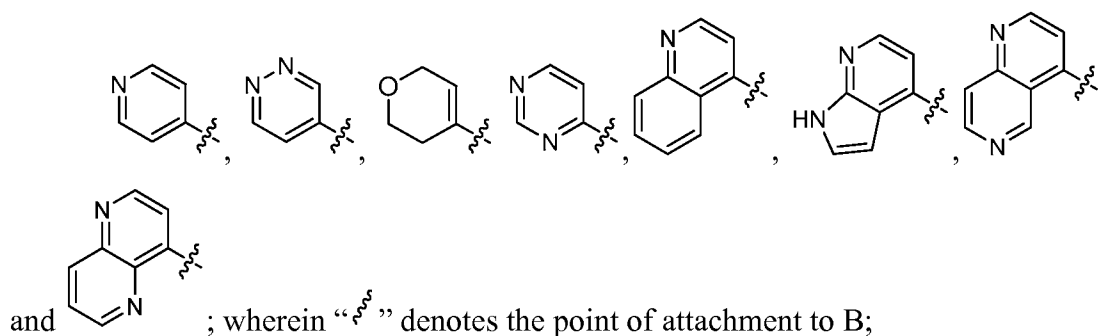
In addition, studies using Huh-7.5 cells indicate a potential utility for AAK1 kinase inhibitors in the treatment of hepatitis C (HCV) infection. Reduction of AAK1 protein using RNA interference mediated gene silencing, treatment with the kinase inhibitor sunitinib (a potent AAK1 inhibitor), and overexpression of Mu2 (AAK1 substrate) phosphorylation site mutant all result in reduced HCV virion assembly. Furthermore the same treatments were shown to inhibit HCV entry, suggesting AAK1 inhibitors can disrupt two host dependent stages of the virus life cycle (Neveu et. al., *PLoS Pathog.* 2012, 8, 1-16; Neveu et. al., *J. Virol.* 2015, posted online 4 February). AAK1 inhibitors may also be useful against HIV and HBV (see, for example, Boge et al., *J. Biol. Chem.* 1998, 273, 15773-15778).

In its first aspect the present disclosure provides a compound of formula (I)
A compound of formula (I)

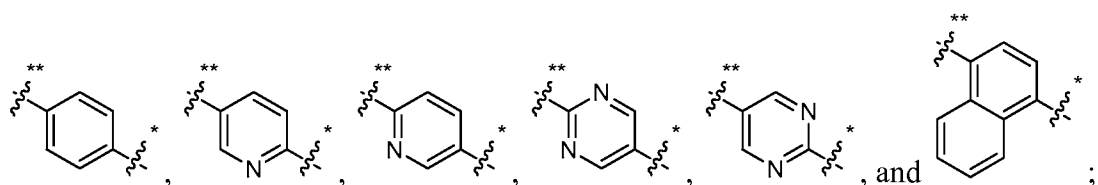


or a pharmaceutically acceptable salt thereof, wherein:

A is selected from



B is selected from



- 5 wherein “*” indicates the point of attachment to R5 and “**” indicates the point of attachment to ring A;

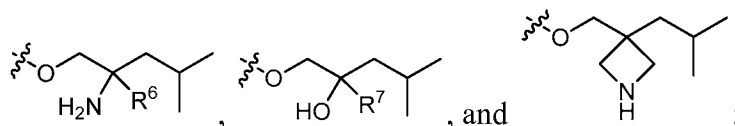
R^1 is selected from hydrogen, amino, $-\text{CO}_2\text{H}$, difluoromethyl, ethyl, halo, hydroxymethyl, methoxy, methyl, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{NHCO}_2\text{CH}_3$, trifluoromethoxy, and trifluoromethyl;

- 10 R^2 is selected from hydrogen, cyano, $-\text{CH}_2\text{OH}$, halo, and methyl;

R^3 is selected from hydrogen, cyano, cyclopropyl, difluoromethyl, halo, hydroxymethyl, methoxy, methyl, methylsulfonyl, trifluoromethoxy, trifluoromethyl, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and a five-membered aromatic ring containing one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

- 15 R^4 is selected from hydrogen, halo, and methyl;

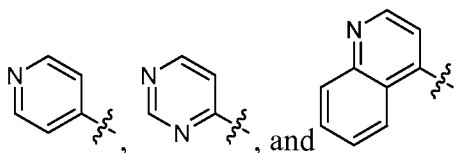
R^5 is selected from



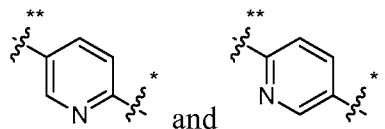
R^6 is selected from hydrogen, ethyl, fluoromethyl, difluoromethyl, methyl, and trifluoromethyl; and

- 20 R^7 is methyl.

In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein A is selected from

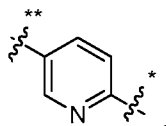


In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein B is selected from

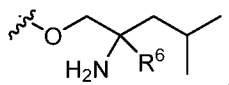


5

In a third embodiment, B is .

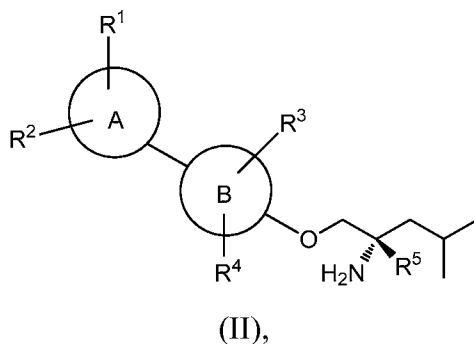


In a fourth embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R⁵ is



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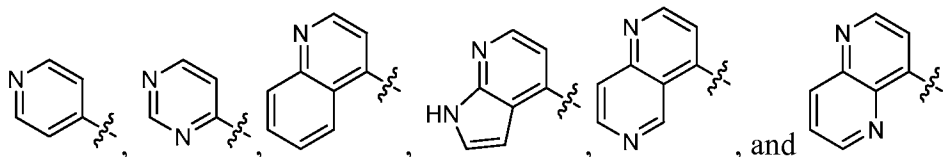
In a second aspect the present disclosure provides a compound of formula (II)



or a pharmaceutically acceptable salt thereof, wherein:

15

A is selected from



wherein “” denotes the point of attachment to B;

B is selected from phenyl and pyridinyl;

R^1 is selected from hydrogen, difluoromethyl, halo, methoxy, methyl, –
NHC(O)CH₃,
-NHCO₂CH₃, and trifluoromethyl;

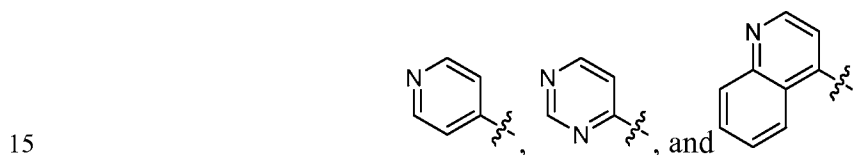
R^2 is selected from hydrogen, -CH₂OH, and halo;

5 R^3 is selected from hydrogen, cyano, cyclopropyl, difluoromethyl, halo, hydroxymethyl, methoxy, methyl, trifluoromethoxy, trifluoromethyl, and a five-membered aromatic ring containing one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

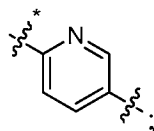
R^4 is selected from hydrogen, halo, and methyl; and

10 R^5 is selected from hydrogen, ethyl, fluoromethyl, difluoromethyl, methyl, and trifluoromethyl.

In a first embodiment of the second aspect the present disclosure provides a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein A is selected from



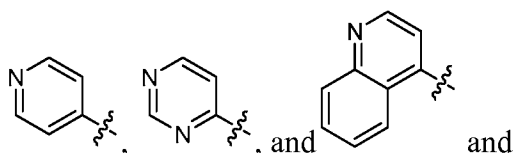
In a second embodiment of the second aspect the present disclosure provides a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein B is pyridinyl. In a third embodiment B is



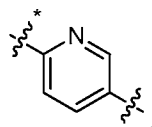
20 wherein “” denotes the point of attachment to A and “” denotes the point of attachment to the oxygen atom.

In a fourth embodiment of the second aspect the present disclosure provides a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein
wherein

25 A is selected from



B is



In a third aspect the present disclosure provides a composition comprising a pharmaceutically acceptable amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a fourth aspect the present disclosure provides a method of inhibiting adaptor associated kinase 1 (AAK1) activity, comprising contacting AAK1 with a compound of formula (I), or a pharmaceutically acceptable salt thereof.

In a fifth aspect the present disclosure provides a method for treating or managing a disease or a disorder mediated by AAK1 activity, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. In a first embodiment of the fifth aspect the disease or disorder is selected from Alzheimer's disease, bipolar disorder, pain, Parkinson's disease, and schizophrenia. In a second embodiment the pain is neuropathic pain. In a third embodiment the neuropathic pain is fibromyalgia or peripheral neuropathy.

Other aspects of the present disclosure may include suitable combinations of embodiments disclosed herein.

Yet other aspects and embodiments may be found in the description provided herein.

BRIEF DESCRIPTION OF THE FIGURES

Aspects of the disclosure are illustrated in Figure 1, which shows results obtained from a formalin pain model using AAK1 homozygous (-/-) knockout mice and their wild-type (+/+) littermates. The AAK1 homozygous (-/-) knockout mice show a clear reduction in both acute and tonic pain response as compared to their wild-type (+/+) littermates.

This disclosure is based, in part, on the discovery that AAK1 knockout mice exhibit a high resistance to pain. That discovery prompted research that ultimately led to the discovery of AAK1 inhibitors, compositions comprising them, and methods of their use.

The description of the present disclosure herein should be construed in congruity with the laws and principals of chemical bonding. In some instances it may be necessary to remove a hydrogen atom in order to accommodate a substituent at any given location.

5 It should be understood that the compounds encompassed by the present disclosure are those that are suitably stable for use as pharmaceutical agent.

As used in the present specification, the following terms have the meanings indicated:

10 All patents, patent applications, and literature references cited in the specification are herein incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

As used herein, the singular forms “a”, “an”, and “the” include plural reference unless the context clearly dictates otherwise.

15 In some instances, the number of carbon atoms in any particular group is denoted before the recitation of the group. For example, the term “C₁₋₆ alkyl” denotes an alkyl group containing one to six carbon atoms. Where these designations exist they supercede all other definitions contained herein.

The term “halo,” as used herein, refers to Br, Cl, F, and/or I.

20 Asymmetric centers may exist in the compounds of the present disclosure. It should be understood that the disclosure encompasses all stereochemical isomeric forms, or mixtures thereof, which possess the ability to inhibit AAK1. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of
25 diastereomers followed by separation or recrystallization, chromatographic techniques, or direct separation of enantiomers on chiral chromatographic columns. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art.

30 Certain compounds of the present disclosure may also exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present disclosure includes each conformational isomer of these compounds and mixtures

thereof.

The term "compounds of the present disclosure", and equivalent expressions, are meant to embrace compounds of formula (I), and pharmaceutically acceptable enantiomers, diastereomers, and salts thereof. Similarly, references to intermediates
5 are meant to embrace their salts where the context so permits.

The present disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon
10 include ^{13}C and ^{14}C . Isotopically-labeled compounds of the disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and
15 reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

The compounds of the present disclosure can exist as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt," as used herein,
20 represents salts or zwitterionic forms of the compounds of the present disclosure which are water or oil-soluble or dispersible, which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended
25 use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting a suitable nitrogen atom with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate; digluconate, dihydrobromide, dihydrochloride, dihydroiodide, glycerophosphate,
30 hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate,

succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids
5 such as oxalic, maleic, succinic, and citric.

Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable
10 salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine,
15 procaine, dibenzylamine, N,N-dibenzylphenethylamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

One embodiment of this disclosure encompasses methods of inhibiting adaptor
20 associated kinase 1 (AAK1), both *in vitro* and *in vivo*, which comprise contacting AAK1 with a compound of formula I or a pharmaceutically acceptable salt thereof.

When it is possible that, for use in therapy, therapeutically effective amounts of a compound of formula (I), as well as pharmaceutically acceptable salts thereof, may be administered as the raw chemical, it is possible to present the active
25 ingredient as a pharmaceutical composition. Accordingly, the disclosure further provides pharmaceutical compositions, which include therapeutically effective amounts of compounds of formula (I) or pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

Unless otherwise indicated, a "therapeutically effective amount" of a compound is an
30 amount sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or

causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent.

The term “therapeutically effective amount,” as used herein, refers to an amount of a compound or compounds sufficient to provide a therapeutic benefit in the treatment or management of a disease or condition, or to delay or minimize one or more symptoms associated with the disease or condition. A “therapeutically effective amount” of a compound means an amount of therapeutic agent, alone or in combination with other therapies, that provides a therapeutic benefit in the treatment or management of the disease or condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of a disease or condition, or enhances the therapeutic efficacy of another therapeutic agent. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially, or simultaneously. The compounds of formula (I) and pharmaceutically acceptable salts thereof, are as described above. The carrier(s), diluent(s), or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the present disclosure there is also provided a process for the preparation of a pharmaceutical formulation including admixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, with one or more pharmaceutically acceptable carriers, diluents, or excipients. The term “pharmaceutically acceptable,” as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, or other problem or complication commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

Pharmaceutical formulations may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Dosage levels of between about 0.01 and about 250 milligram per kilogram ("mg/kg") body weight per day, preferably between about 0.05 and about 100 mg/kg body weight per day of the compounds of the present disclosure are typical in a monotherapy for the prevention

and treatment of disease. Typically, the pharmaceutical compositions of this disclosure will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending on the condition being treated, the severity of the condition, the time of administration, the route of administration, the rate of excretion of the compound employed, the duration of treatment, and the age, gender, weight, and condition of the patient. Preferred unit dosage formulations are those containing a daily dose or sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient. Treatment may be initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compound is most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

When the compositions of this disclosure comprise a combination of a compound of the present disclosure and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent are usually present at dosage levels of between about 10 to 150%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

Compounds of the disclosure may be administered in combination with one or more additional therapeutic or prophylactic agents. For example, when used for the treatment of pain, possible additional agents include immunosuppressive agents, anti-inflammatory agents, and/or other agents used in the treatment of pain.

Immunosuppressants suitable for use in the methods and compositions of this disclosure include those known in the art. Examples include aminopterin, azathioprine, cyclosporin A, D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate, minocycline, rapamycin, sulfasalazine, tacrolimus (FK506), and pharmaceutically acceptable salts thereof. A particular immunosuppressant is methotrexate.

Additional examples of immunosuppressants include anti-TNF antibodies, such as adalimumab, certolizumab pegol, etanercept, and infliximab. Others include interleukin-1 blockers, such as anakinra. Others include anti-B cell (CD20)

antibodies, such as rituximab. Others include T cell activation blockers, such as abatacept.

Other immunosuppressants include inosine monophosphate dehydrogenase inhibitors, such as mycophenolate mofetil (CellCept®) and mycophenolic acid
5 (Myfortic®).

Anti-inflammatory drugs suitable for use in the methods and compositions of this disclosure include those known in the art. Examples include glucocorticoids and NSAIDs. Examples of glucocorticoids include aldosterone, beclometasone, betamethasone, cortisone, deoxycorticosterone, dexamethasone, fludrocortisone,
10 hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, and pharmaceutically acceptable salts thereof.

Examples of NSAID include salicylates (*e.g.*, aspirin, amoxiprin, benorilate, choline magnesium salicylate, diflunisal, faislamine, methyl salicylate, magnesium salicylate, salicyl salicylate, and pharmaceutically acceptable salts thereof),
15 arylalkanoic acids (*e.g.*, diclofenac, aceclofenac, acemetacin, bromfenac, etodolac, indometacin, nabumetone, sulindac, tolmetin, and pharmaceutically acceptable salts thereof), arylpropionic acids (*e.g.*, ibuprofen, carprofen, fenbufen, fenoprofen, flurbiprofen, ketoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, tiaprofenic acid, suprofen, and pharmaceutically acceptable salts thereof), arylanthranilic acids
20 (*e.g.*, meclofenamic acid, mefenamic acid, and pharmaceutically acceptable salts thereof), pyrazolidine derivatives (*e.g.*, azapropazone, metamizole, oxyphenbutazone, phenylbutazone, sulfinprazone, and pharmaceutically acceptable salts thereof), oxicams (*e.g.*, lornoxicam, meloxicam, piroxicam, tenoxicam, and pharmaceutically acceptable salts thereof), COX-2 inhibitors (*e.g.*, celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, and pharmaceutically acceptable salts thereof), and
25 sulphonanilides (*e.g.*, nimesulide and pharmaceutically acceptable salts thereof).

Other agents used in the treatment of pain (including but not limited to neuropathic and inflammatory pain) include, but are not limited to, agents such as pregabalin, lidocaine, duloxetine, gabapentin, carbamazepine, capsaicin, and other
30 serotonin/norepinephrine/dopamine reuptake inhibitors, and opiates (such as oxycontin, morphine, and codeine).

In the treatment of pain caused by a known disease or condition, such as diabetes, infection (*e.g.*, herpes zoster or HIV infection), or cancer, compounds of the

disclosure may be administered in combination with one or more additional therapeutic or prophylactic agents directed at the underlying disease or condition. For example, when used to treat diabetic neuropathy, compounds of the disclosure may be administered in combination with one or more anti-diabetic agents, anti-
5 hyperglycemic agents, hypolipidemic/lipid lowering agents, anti-obesity agents, anti-hypertensive agents and appetite suppressants. Examples of anti-diabetic agents include biguanides (*e.g.*, metformin, phenformin), glucosidase inhibitors (*e.g.*, acarbose, miglitol), insulins (including insulin secretagogues and insulin sensitizers), meglitinides (*e.g.*, repaglinide), sulfonylureas (*e.g.*, glimepiride, glyburide, gliclazide,
10 chlorpropamide, and glipizide), biguanide/glyburide combinations (*e.g.*, Glucovance), thiazolidinediones (*e.g.*, troglitazone, rosiglitazone, and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1) or other agonists of the GLP-1 receptor, dipeptidyl
15 peptidase IV (DPP4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors (*e.g.*, dapagliflozin, canagliflozin, and LX-4211).

Pharmaceutical formulations may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual, or transdermal), vaginal, or parenteral
20 (including subcutaneous, intracutaneous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional, intravenous, or intradermal injections or infusions) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Oral administration or administration by injection are
25 preferred.

Pharmaceutical formulations adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil emulsions.

30 For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a

similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing, and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and
5 filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate, or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate, or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

10 Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, and the like.
15 Lubricants used in these dosage forms include sodium oleate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, betonite, xanthan gum, and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant, and pressing into tablets. A powder mixture is prepared by mixing the
20 compound, suitable comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelating, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or and absorption agent such as betonite, kaolin, or dicalcium phosphate. The powder mixture can be granulated by wetting with a
25 binder such as syrup, starch paste, acadia mucilage, or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a
30 stearate salt, talc, or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present disclosure can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a

sealing coat of shellac, a coating of sugar or polymeric material, and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups, and elixirs can be prepared in dosage unit
5 form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxyethylene sorbitol ethers, preservatives, flavor additive such as peppermint oil
10 or natural sweeteners, or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers,
15 wax, or the like.

The compounds of formula (I), and pharmaceutically acceptable salts thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol,
20 stearylamine, or phosphatidylcholines.

The compounds of formula (I) and pharmaceutically acceptable salts thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include
25 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters,
30 polyacetals, polydihydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.

Pharmaceutical formulations adapted for transdermal administration may be presented as discrete patches intended to remain in intimate contact with the

epidermis of the recipient for a prolonged period of time. For example, the active ingredient may be delivered from the patch by iontophoresis as generally described in *Pharmaceutical Research* 1986, 3(6), 318.

Pharmaceutical formulations adapted for topical administration may be
5 formulated as ointments, creams, suspensions, lotions, powders, solutions, pastes, gels, sprays, aerosols, or oils.

Pharmaceutical formulations adapted for rectal administration may be presented as suppositories or as enemas.

Pharmaceutical formulations adapted for nasal administration wherein the
10 carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns which is administered in the manner in which snuff is taken, *i.e.*, by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as a nasal spray or nasal drops, include aqueous or oil solutions of the
15 active ingredient.

Pharmaceutical formulations adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers, or insufflators.

Pharmaceutical formulations adapted for vaginal administration may be
20 presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulations.

Pharmaceutical formulations adapted for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions
25 which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared
30 from sterile powders, granules, and tablets.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for

oral administration may include flavoring agents.

The term "patient" includes both human and other mammals.

Unless otherwise indicated, the terms "manage," "managing", and "management" encompass preventing the recurrence of the specified disease or disorder in a patient who has already suffered from the disease or disorder, and/or lengthening the time that a patient who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a patient responds to the disease or disorder.

The term "treating" refers to: (i) preventing a disease, disorder or condition from occurring in a patient that may be predisposed to the disease, disorder, and/or condition but has not yet been diagnosed as having it; (ii) inhibiting the disease, disorder, or condition, i.e., arresting its development; and (iii) relieving the disease, disorder, or condition, i.e., causing regression of the disease, disorder, and/or condition.

This disclosure is intended to encompass compounds having Formula (I) when prepared by synthetic processes or by metabolic processes including those occurring in the human or animal body (*in vivo*) or processes occurring *in vitro*.

EXAMPLES

The present disclosure will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present disclosure covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present disclosure, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

The abbreviations used in the present application, including particularly in the illustrative schemes and examples which follow, are well-known to those skilled in the art. Some of the abbreviations used are as follows: MeOH for methanol; min for minutes, EtOAc or ETOAC for ethyl acetate; h or hr or hrs for hours; Ph₃P for triphenylphosphine, DIAD for diisopropyl azodicarboxylate; RT or rt or r.t. for room

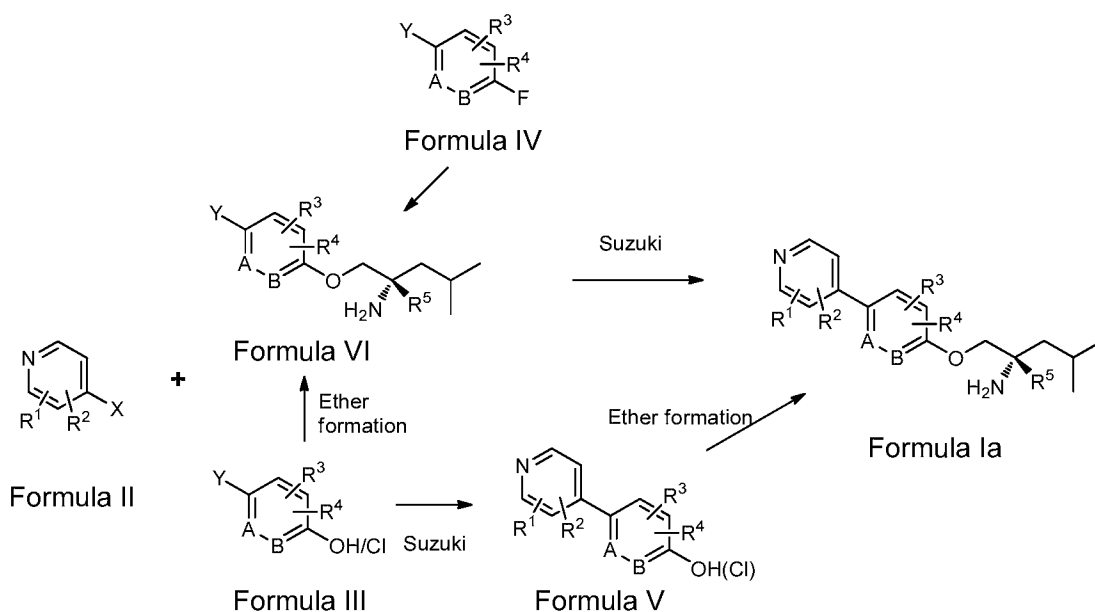
temperature or retention time (context will dictate); t_R for retention time; EtOH for ethanol; DMSO for dimethylsulfoxide; THF for tetrahydrofuran; dppf for diphenylphosphinoferrocene; TFA for trifluoroacetic acid; NMP for *N*-methylpyrrolidine; CBz or Cbz for benzyloxycarbonyl; DCM for dichloromethane; IPA for isopropyl alcohol; DMAP for *N,N*-dimethylaminopyridine; BOC or Boc for *tert*-butoxycarbonyl; (BOC)₂O for di-*tert*-butyl dicarbonate/ DMF for *N,N*-dimethylformamide; OAc for acetate; Cbz for carbobenzyloxy; TMS for trimethylsilane; LDA for lithium diisopropylamide; MOM-Cl for chloromethyl methyl ether; KHMDS for potassium hexamethyldisilazide; KOtBu for potassium *tert*-butoxide; DAST for diethylaminosulfur trifluoride; BuOH for *n*-butanol; *n*-BuLi for *n*-butyllithium; and NBS for *N*-bromosuccinimide.

The compounds of the present disclosure may be prepared using the reactions and techniques described in this section as well as other synthetic methods known to those of ordinary skill in the art. The reactions are performed in solvents appropriate to the reagents and materials employed and suitable for the transformation being affected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvents, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

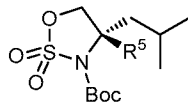
Compounds of Formula Ia can be synthesized following General Scheme I. The two key reactions, Suzuki coupling and ether formation, could alternate as shown depending on the commercially available starting materials. The Suzuki coupling substrates, boronic acids/boronates, were either commercially available or prepared from corresponding halogen intermediates (Cl/Br/I) with various standard literature conditions. The ether formation can be achieved by S_NAR when a fluorine intermediate (Formula IV) is available, by Mitsunobu reaction or alkylation with suitable amino alcohol when an OH is available (Formula III/V), and by Buchwald's Pd-catalyzed ether formation reaction when a Cl intermediate (Formula III/V) is

available. In cases where R^5 is bigger than H, an activated form of the amino alcohol (Formula VII) was used as the OH-alkylating reagent. Sometimes NH_2 and OH were protected and deprotected during the reaction sequence.

5 General Scheme I:



$X/Y = Cl, Br, I$ or Boronic acid/boronate; $A/B = C$ or N (phenyl or pyridine).



Formula VII

A common activated amino alcohol reagent for ether formation when R^5 is not H.

In the following examples, proton NMR spectra were recorded on either a Bruker 400 or 500 MHz NMR spectrometer. Chemical shifts are reported in δ values relative to tetramethylsilane. Liquid chromatography (LC)/mass spectra were run on a Shimadzu LC coupled to a Waters Micromass ZQ using at least one of the following methods.

LC/MS Method A:

Column : Phenomenex LUNA C18, 30x2, 3 μ m; Solvent A = 5 % MeOH: 95% Water:10mM Ammonium Acetate; Solvent B = 95% MeOH:5% Water:10mM

Ammonium Acetate; Flow rate: 1 ml/min; Starting B = 0%; Final B = 100%;
Gradient time = 2 min; Run time: 3 min.

LC/MS Method B:

- 5 Column : Phenomenex LUNA C18, 30x2, 3 μ m; Solvent A = 10 % MeOH: 90%
Water:0.1%TFA; Solvent B = 90% MeOH:10% Water:0.1%TFA; Flow rate: 1
ml/min; Starting B = 0%; Final B = 100%; Gradient time = 2 min; Run time: 3 min.

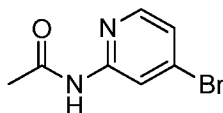
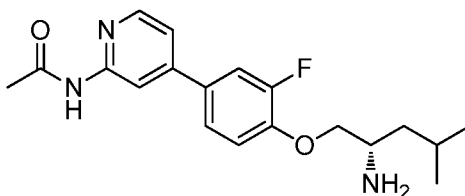
LC/MS Method C:

- 10 Column : Phenomenex LUNA C18, 30x2, 3 μ m; Solvent A = 5 % MeOH: 95%
Water:10mM Ammonium Acetate; Solvent B = 95% MeOH:5% Water:10mM
Ammonium Acetate; Flow rate: 0.8 ml/min; Starting B = 0%; Final B = 100%;
Gradient time = 4 min; Run time: 5 min.

15

Example 1

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

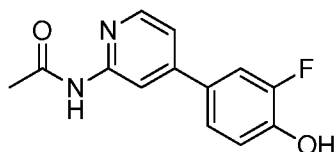


20

Part A: N-(4-bromopyridin-2-yl)acetamide

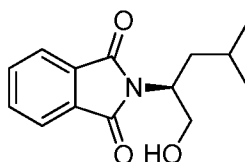
- To a mixture of 4-bromopyridin-2-amine (3.11 g, 17.98 mmol) in CH₂Cl₂ (60 mL) at 0 °C was added acetyl chloride (1.406 mL, 19.77 mmol) and pyridine (1.745 mL, 21.57 mmol). The mixture was warmed to rt and stirred for 2 h. The reaction
25 was quenched with water and diluted with EtOAc. The layers were separated. The organic layer was washed with water, brine, dried (Na₂SO₄) and concentrated under reduced pressure to obtain *N*-(4-bromopyridin-2-yl)acetamide (3.82 g, 17.05 mmol, 95% yield) as a white solid. The material was carried on without further purification.

LCMS (ESI) m/e 215.0 $[(M+H)^+]$, calcd $C_7H_8Br_1N_2O_1$, 215.0]; LC/MS retention time (method A): t_R = 2.61 min.



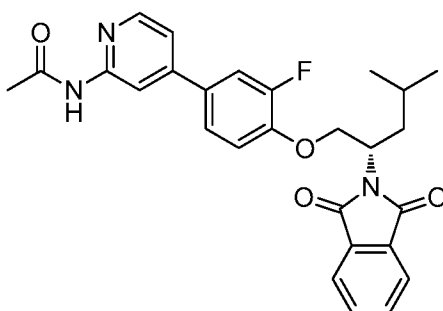
5 *Part B: N-(4-(3-fluoro-4-hydroxyphenyl)pyridin-2-yl)acetamide*

To a 15 mL vial was added *N*-(4-bromopyridin-2-yl)acetamide (205.8 mg, 0.957 mmol), (3-fluoro-4-hydroxyphenyl)boronic acid (239 mg, 1.531 mmol), and Na_2CO_3 (1.435 mL, 2.87 mmol) in dioxane (3 mL) under nitrogen to give a colorless solution. 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene
 10 (39.4 mg, 0.048 mmol) was added under nitrogen. The vial was sealed and heated at 130 °C (microwave) for 2 h. The mixture was partitioned between water and EtOAc. The layers were separated. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to obtain *N*-(4-(3-fluoro-4-hydroxyphenyl)pyridin-2-yl)acetamide (200 mg, 0.812 mmol, 85% yield) as a tan
 15 solid. LCMS (ESI) m/e 247.0 $[(M+H)^+]$, calcd $C_{13}H_{12}F_1N_2O_2$, 247.1]; LC/MS retention time (method A): t_R = 1.51 min.



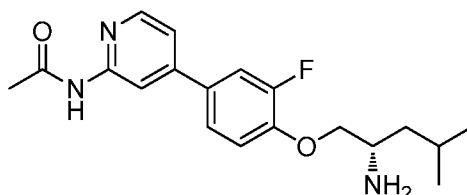
Part C: (S)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione

20 To a 250 mL round-bottomed flask was added (*S*)-3-amino-5-methylhexan-1-ol (2.166 g, 16.51 mmol) and isobenzofuran-1,3-dione (2.445 g, 16.51 mmol) in toluene (60 mL) to give a colorless suspension. The mixture was heated at 110 °C for 16 h. The volatiles were removed under high vacuum to afford (*S*)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione (4.08 g, 16.51 mmol, quantitative yield)
 25 as a light yellow dense oil. LCMS (ESI) m/e 246.2 $[(M-H)^+]$, calcd $C_{14}H_{16}N_1O_3$, 246.1]; LC/MS retention time (method A): t_R = 1.88 min.



Part D: (S)-N-(4-(4-((2-(1,3-dioxoisindolin-2-yl)-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

To a 50 mL round-bottomed flask was added (*S*)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione (93 mg, 0.375 mmol), Ph₃P (123 mg, 0.468 mmol), and (*S*)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione (93 mg, 0.375 mmol) in tetrahydrofuran (1 mL) to give a tan suspension. DIAD (0.091 mL, 0.468 mmol) was added dropwise at rt. The resultant clear tan solution was stirred at rt for 19 h. The solution was concentrated under reduced pressure to give a tan oil which was carried directly into the next reaction. LCMS (ESI) *m/e* 476.3 [(M+H)⁺, calcd C₂₇H₂₇F₁N₃O₄, 476.2]; LC/MS retention time (method A): *t_R* = 2.21 min.



Part E: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

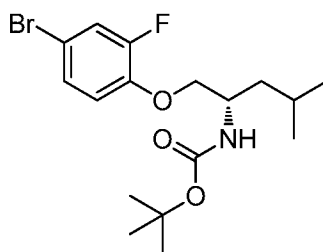
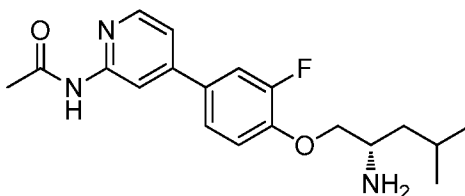
To a 50 mL round-bottomed flask was added (*S*)-*N*-(4-(4-((2-(1,3-dioxoisindolin-2-yl)-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide (148 mg, 0.312 mmol) in EtOH (2 mL) to give a tan solution. Hydrazine (0.049 mL, 1.560 mmol) was added and the mixture was heated at 60 °C for 2 h. The solution was cooled to rt and was concentrated under reduced pressure. The residue was suspended in MeOH, filtered, and purified by prep-HPLC (24 mg, 0.069 mmol, 22% yield for 3 steps): ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.53 (s, 1H), 8.33 (d, *J* = 4.9 Hz, 2H), 7.61 (dd, *J* = 12.5, 2.2 Hz, 1H), 7.52 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.32 (t, *J* = 8.7 Hz, 1H), 3.97 (dd, *J* = 9.5, 4.9 Hz, 1H), 3.90 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.12 (dt, *J* = 11.9, 5.4 Hz, 1H), 2.12 (s, 3H), 1.81 (dq, *J* = 13.0, 6.5 Hz,

1H), 1.33 (ddd, $J = 13.5, 8.5, 5.0$ Hz, 1H), 1.26 (ddd, $J = 13.5, 8.5, 5.5$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H); LCMS (ESI) m/e 346.2 $[(M+H)^+]$, calcd $C_{19}H_{25}F_1N_3O_2$, 346.2]; LC/MS retention time (method A): $t_R = 1.89$ min.

5

Alternative Synthesis of Example 1

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

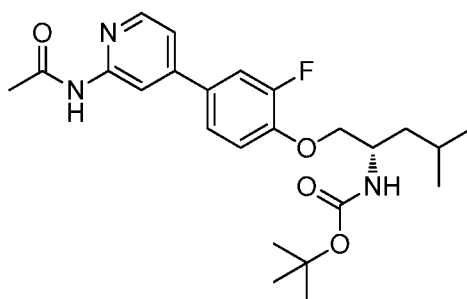


10

Part 2A: (S)-tert-butyl (1-(4-bromo-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate

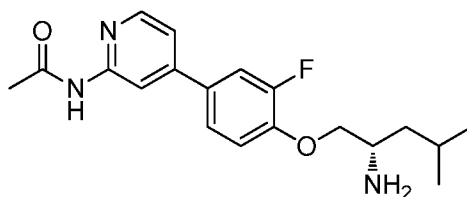
To a 15 mL vial was added (*S*)-*tert*-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (172 mg, 0.792 mmol), Ph_3P (260 mg, 0.990 mmol), and 4-bromo-2-fluorophenol (126 mg, 0.660 mmol) in tetrahydrofuran (2mL) to give a tan solution. DIAD (0.180 mL, 0.924 mmol) was added at rt. The resulted clear tan solution was stirred at rt for 16 h. The solution was concentrated under reduced pressure to afford a tan oil which was directly purified by silica gel column chromatography (up to 60% EtOAc/hexane to afford (*S*)-*tert*-butyl (1-(4-bromo-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate (249 mg, 0.638 mmol, 97% yield) as a colorless oil: ^1H NMR (400 MHz, Chloroform- d) δ 7.24 (dd, $J = 10.5, 2.4$ Hz, 1H), 7.21 - 7.16 (m, 1H), 6.90 - 6.81 (m, 1H), 4.83 - 4.69 (m, 1H), 4.08 - 3.92 (m, 3H), 1.71 (dp, $J = 13.2, 6.6$ Hz, 1H), 1.59 - 1.49 (m, 2H), 1.47 (d, $J = 3.8$ Hz, 9H), 0.96 (dd, $J = 6.6, 4.4$ Hz, 6H); LCMS (ESI) m/e 412.1 $[(M+Na)^+]$, calcd $C_{17}H_{25}BrFNNaO_3$, 412.1]; LC/MS retention time (method B): $t_R = 2.41$ min.

25



Part 2B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate

To a 15 mL vial was added *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (208 mg, 0.792 mmol), (*S*)-*tert*-butyl (1-(4-bromo-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate (258 mg, 0.66 mmol), and Na₂CO₃ (0.990 mL, 1.980 mmol) in dioxane (2 mL) under nitrogen to give a colorless suspension. 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene (27.1 mg, 0.033 mmol) was added under nitrogen. The vial was sealed and heated at 130 °C (microwave) for 2 h. The mixture was diluted with water and EtOAc. The layers were separated. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. The residue was purified by silica gel column chromatography (up to 70% EtOAc/hexane) to afford the desired product (200 mg, 0.449 mmol, 68% yield for two steps) as a colorless oil: ¹H NMR (400 MHz, Chloroform-d) δ 8.79 (s, 1H), 8.46 (s, 1H), 8.29 (d, *J* = 5.4 Hz, 1H), 7.50 - 7.38 (m, 2H), 7.21 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 1H), 4.81 (d, *J* = 9.2 Hz, 1H), 4.12 - 3.96 (m, 3H), 2.25 (s, 3H), 1.74 (dq, *J* = 13.5, 6.5, 6.1 Hz, 1H), 1.63 - 1.52 (m, 2H), 1.47 (s, 9H), 0.98 (dd, *J* = 6.6, 3.3 Hz, 6H); LCMS (ESI) *m/e* 446.2 [(*M*+*H*)⁺, calcd C₂₄H₃₃F₁N₃O₄, 446.2]; LC/MS retention time (method B): *t*_R = 2.11 min.



Part 2C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

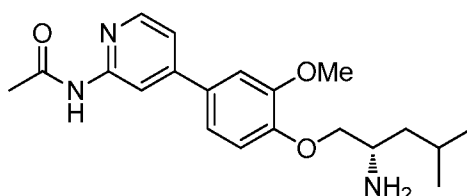
To a 50 mL round-bottomed flask was added (*S*)-*tert*-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate (202 mg,

0.453 mmol) in dichloromethane (2 mL) to give a colorless solution. TFA (0.5 mL) was added, and the resulted tan solution was stirred at rt for 1 h. The volatiles were removed under reduced pressure. The residue was diluted with EtOAc and basified with 1N NaOH. The layers were separated. The organic layer was washed with
 5 brine, dried (Na₂SO₄) and concentrated under reduced pressure to afford (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide (155 mg, 0.449 mmol, 99% yield) as a slightly tan oil: ¹H NMR and LCMS matched that of the previously prepared; ¹⁹F NMR (376 MHz, Chloroform-d) δ -133.47.

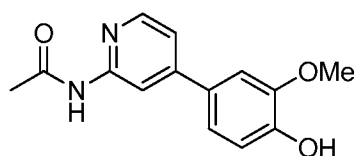
10

Example 2

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide

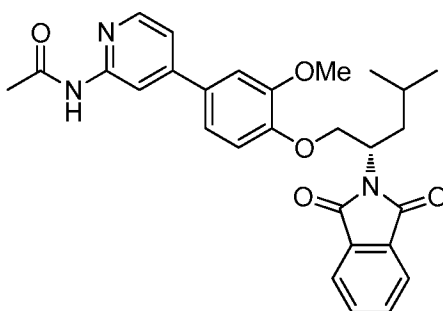


15 Prepared as described in Example 1.



Part A: N-(4-(3-methoxy-4-hydroxyphenyl)pyridin-2-yl)acetamide

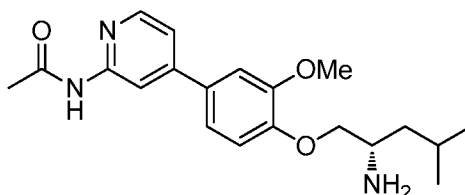
LCMS (ESI) *m/e* 259.1 [(M+H)⁺, calcd C₁₄H₁₅N₂O₃, 259.3]; LC/MS retention
 20 time (method A): *t*_R = 1.51 min.



Part B: (S)-N-(4-(4-((2-(1,3-dioxoisindolin-2-yl)-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide

LCMS (ESI) m/e 488.3 [(M+H)⁺, calcd C₂₈H₃₀N₃O₅, 488.2]; LC/MS retention time (method A): t_R = 2.17 min.

5

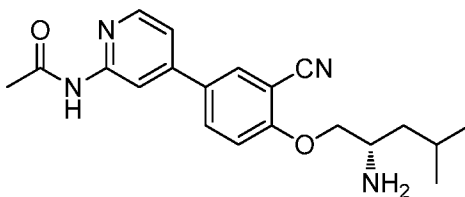


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide.

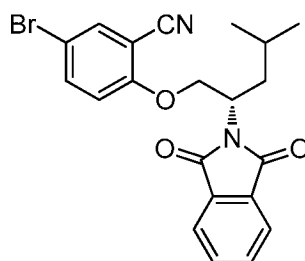
Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide (14.9 mg, 0.042 mmol, 80% yield for final
 10 step) as a slightly tan foam: ¹H NMR (500 MHz, DMSO-d₆) δ 10.50 (s, 1H), 8.35 (s, 1H), 8.32 (d, J = 5.2 Hz, 1H), 7.40 (dd, J = 5.2, 1.8 Hz, 1H), 7.32 - 7.22 (m, 2H), 7.12 (d, J = 8.2 Hz, 1H), 3.90 (dd, J = 9.3, 4.6 Hz, 1H), 3.87 (s, 3H), 3.78 (dd, J = 9.4, 6.9 Hz, 1H), 3.09 (p, J = 5.5, 5.1 Hz, 1H), 2.12 (s, 3H), 1.82 (dt, J = 13.4, 6.7
 15 Hz, 1H), 1.32 (ddd, J = 13.5, 8.6, 5.0 Hz, 1H), 1.24 (ddd, J = 13.6, 8.7, 5.5 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H); LCMS (ESI) m/e 358.2 [(M+H)⁺, calcd C₂₀H₂₈N₃O₃, 358.2]; LC/MS retention time (method A): t_R = 1.70 min.

Example 3

20 (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide



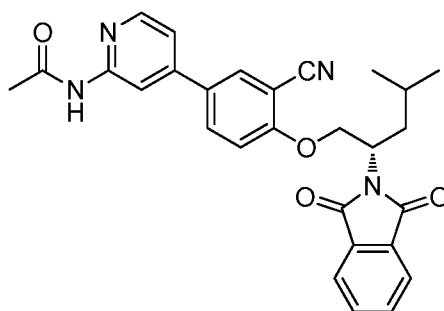
Prepared as described in Example 1.



Part A: (S)-5-bromo-2-((2-(1,3-dioxoisindolin-2-yl)-4-methylpentyl)oxy)benzonitrile.

¹H NMR (400 MHz, Chloroform-d) δ 7.86 (dd, $J = 5.4, 3.0$ Hz, 2H), 7.74 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.63 - 7.55 (m, 2H), 6.87 (d, $J = 8.8$ Hz, 1H), 4.85 (tdd, $J = 9.8, 5.6, 3.9$ Hz, 1H), 4.57 (t, $J = 9.2$ Hz, 1H), 4.32 (dd, $J = 9.3, 5.7$ Hz, 1H), 2.28 - 2.14 (m, 1H), 1.66 - 1.53 (m, 2H), 1.00 (d, $J = 5.8$ Hz, 3H), 0.96 (d, $J = 6.0$ Hz, 3H); LCMS (ESI) m/e 427.1 [(M+H)⁺, calcd C₂₁H₂₀BrN₂O₃, 427.1]; LC/MS retention time (method B): $t_R = 2.29$ min.

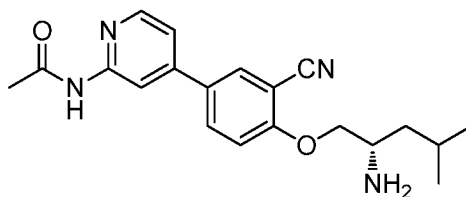
10



Part B: (S)-N-(4-(3-cyano-4-((2-(1,3-dioxoisindolin-2-yl)-4-methylpentyl)oxy)phenyl)pyridin-2-yl)acetamide.

LCMS (ESI) m/e 483.3 [(M+H)⁺, calcd C₂₈H₂₇N₄O₄, 483.2]; LC/MS retention time (method B): $t_R = 2.06$ min.

15



Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide

Acetamide was partially hydrolyzed (see Example 4) and the two products were separated and identified. Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-

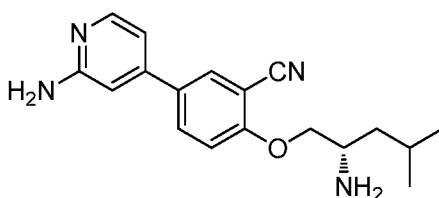
20

3-cyanophenyl)pyridin-2-yl)acetamide (10.1 mg, 0.028 mmol, 23% yield) as a colorless foam. ¹H NMR (500 MHz, DMSO-d₆) δ 10.58 (s, 1H), 8.39 - 8.32 (m, 2H), 8.12 (d, *J* = 2.5 Hz, 1H), 8.00 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 4.05 (dd, *J* = 9.3, 5.0 Hz, 1H), 3.99 (t, *J* = 7.9 Hz, 1H), 3.12 (s, 1H), 2.13 (s, 3H), 1.84 (p, *J* = 6.6 Hz, 1H), 1.42 - 1.31 (m, 1H), 1.27 (dq, *J* = 14.0, 7.0, 6.2 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H); LCMS (ESI) *m/e* 353.2 [(M+H)⁺, calcd C₂₀H₂₅N₄O₂, 353.2]; LC/MS retention time (method B): *t*_R = 1.44 min.

10

Example 4

(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-aminopyridin-4-yl)benzonitrile

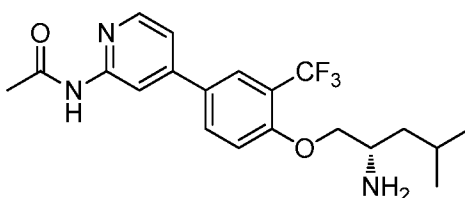


The hydrolyzed material from Example 3 was identified as (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-aminopyridin-4-yl)benzonitrile (10.1 mg, 0.030 mmol, 26% yield) as a colorless foam. ¹H NMR (500 MHz, DMSO-d₆) δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 5.3 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 6.82 (dd, *J* = 5.3, 1.6 Hz, 1H), 6.70 (s, 1H), 5.97 (s, 2H), 4.03 (dd, *J* = 9.3, 5.1 Hz, 1H), 3.96 (t, *J* = 7.7 Hz, 1H), 3.10 (s, 1H), 1.84 (p, *J* = 6.4 Hz, 1H), 1.35 (q, *J* = 9.3, 6.6 Hz, 1H), 1.26 (dq, *J* = 13.7, 6.8, 6.1 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); LCMS (ESI) *m/e* 311.2 [(M+H)⁺, calcd C₁₈H₂₃N₄O₁, 311.2]; LC/MS retention time (method B): *t*_R = 1.35 min.

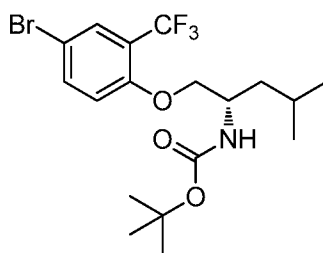
25

Example 5

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

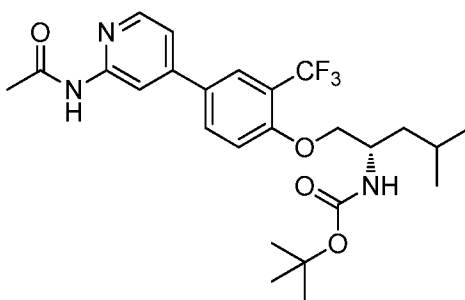


Prepared as described in Example 1.



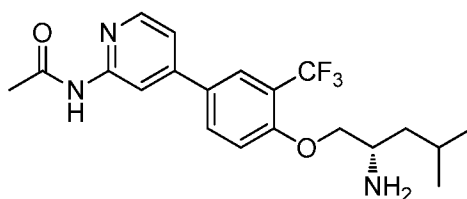
Part A: (S)-tert-butyl (1-(4-bromo-2-(trifluoromethyl)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 7.67 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 8.8, 2.5 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.71 (d, J = 8.3 Hz, 1H), 4.03 (p, J = 7.2 Hz, 3H), 1.68 (hept, J = 6.7 Hz, 1H), 1.55 - 1.48 (m, 2H), 1.44 (s, 9H), 0.95 (dd, J = 6.6, 4.2 Hz, 6H); LCMS (ESI) m/e 462.1 [(M+Na)⁺, calcd C₁₈H₂₅BrF₃N₁Na₁O₃, 462.1]; LC/MS retention time (method B): t_R = 2.45 min.



Part B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-(trifluoromethyl)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 9.50 (s, 1H), 8.48 (s, 1H), 8.29 (d, J = 5.3 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H), 7.81 (dd, J = 8.5, 2.4 Hz, 1H), 7.21 (dd, J = 5.3, 1.7 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 4.79 (d, J = 8.7 Hz, 1H), 4.13 - 4.04 (m, 3H), 2.25 (s, 3H), 1.70 (dt, J = 13.6, 6.9 Hz, 1H), 1.54 (t, J = 7.2 Hz, 2H), 1.44 (s, 9H), 0.96 (d, J = 2.8 Hz, 3H), 0.95 (d, J = 2.7 Hz, 3H); LCMS (ESI) m/e 496.2 [(M+H)⁺, calcd C₂₅H₃₃F₃N₃O₄, 446.2]; LC/MS retention time (method A): t_R = 2.28 min.

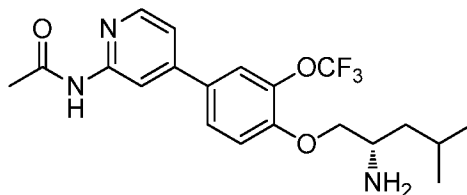


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

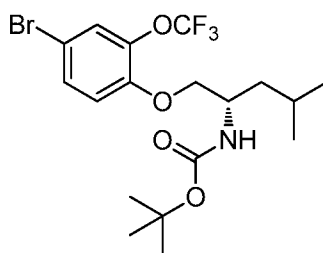
(221 mg, 0.531 mmol, quantitative yield for final step) as a white foam. ¹H NMR (400 MHz, Chloroform-d) δ 9.15 (s, 1H), 8.48 (s, 1H), 8.30 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.23 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 4.08 (dd, *J* = 8.7, 3.6 Hz, 1H), 3.85 (dd, *J* = 8.7, 7.1 Hz, 1H), 3.32 (qd, *J* = 7.0, 3.6 Hz, 1H), 2.25 (s, 3H), 1.80 (dp, *J* = 13.5, 6.7 Hz, 1H), 1.57 (s, 2H), 1.38 (t, *J* = 7.0 Hz, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -62.40; LCMS (ESI) *m/e* 394.2 [(M-H)⁻, calcd C₂₀H₂₃F₃N₃O₂, 394.2]; LC/MS retention time (method A): *t_R* = 1.97 min.

Example 6

(S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide

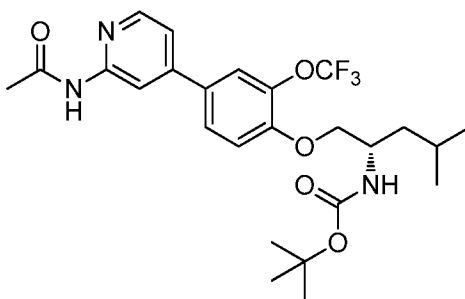


Prepared as described in Example 1.



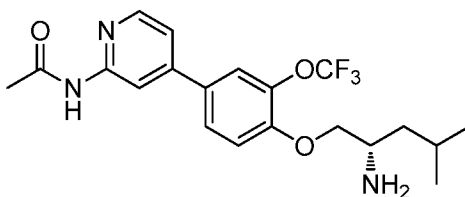
Part A: (*S*)-*tert*-butyl (1-(4-bromo-2-(trifluoromethoxy)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 - 7.33 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.78 - 4.61 (m, 1H), 4.09 - 3.90 (m, 3H), 1.68 (dq, *J* = 13.3, 6.7 Hz, 1H),
 5 1.51 (t, *J* = 6.8 Hz, 2H), 1.45 (s, 9H), 0.95 (dd, *J* = 6.6, 5.4 Hz, 6H); LCMS (ESI) *m/e* 478.1 [(*M*+Na)⁺, calcd C₁₈H₂₅BrF₃N₁Na₁O₄, 478.0]; LC/MS retention time (method B): *t*_R = 2.45 min.



10 Part B: (*S*)-*tert*-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-(trifluoromethoxy)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.13 (s, 1H), 8.47 (s, 1H), 8.29 (d, *J* = 5.3 Hz, 1H), 7.61 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.56 (q, *J* = 1.3 Hz, 1H), 7.21 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 4.77 (d, *J* = 8.3 Hz, 1H), 4.12 - 3.98 (m,
 15 3H), 2.25 (s, 3H), 1.73 (dq, *J* = 13.7, 7.1, 6.4 Hz, 1H), 1.55 (t, *J* = 7.0 Hz, 2H), 1.46 (s, 9H), 0.97 (dd, *J* = 6.6, 4.1 Hz, 6H); LCMS (ESI) *m/e* 512.2 [(*M*+H)⁺, calcd C₂₅H₃₃F₃N₃O₅, 512.2]; LC/MS retention time (method A): *t*_R = 2.29 min.



20 Part C: (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide

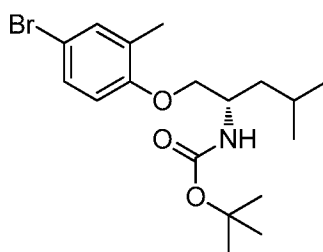
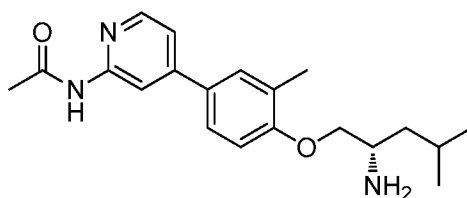
(225 mg, 0.520 mmol, 95% yield for final step) as a white foam. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.59 (s, 1H), 8.47 (s, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 7.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 5.4, 1.7 Hz, 1H),
 25 7.04 (d, *J* = 8.6 Hz, 1H), 4.00 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.80 (dd, *J* = 8.8, 7.3 Hz,

1H), 3.31 (qd, $J = 7.1, 3.7$ Hz, 1H), 2.23 (s, 3H), 1.86 - 1.72 (m, $J = 6.9$ Hz, 1H), 1.63 (s, 2H), 1.35 (t, $J = 7.0$ Hz, 2H), 0.95 (dd, $J = 9.1, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, Chloroform- d) δ -58.10; LCMS (ESI) m/e 412.1 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{20}\text{H}_{25}\text{F}_3\text{N}_3\text{O}_3$, 412.2]; LC/MS retention time (method A): $t_R = 1.99$ min.

5

Example 7

(*S*)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)acetamide

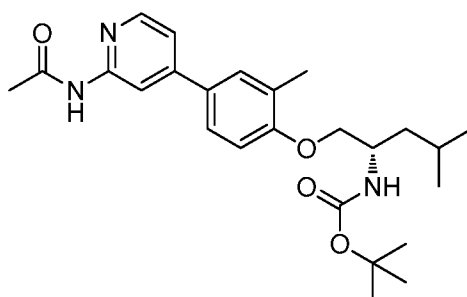


10

Part A: (*S*)-tert-butyl (1-(4-bromo-2-methylphenoxy)-4-methylpentan-2-yl)carbamate

DIAD (0.090 mL, 0.464 mmol) was added to a solution of triphenylphosphine (0.097 g, 0.371 mmol), 4-bromo-2-methylphenol (0.069 g, 0.371 mmol) and (*S*)-tert-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (0.0672 g, 0.309 mmol) in THF (1.5 mL) at rt under N_2 . The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure. The residue was purified via silica gel chromatography (0 to 25% ethyl acetate in hexanes). NMR and LCMS showed the product contained the starting material (4-bromo-2-methoxyphenol). This mixture was taken up in ethyl acetate and washed with 1N NaOH (2X) and water (1X). The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give (*S*)-tert-butyl (1-(4-bromo-2-methylphenoxy)-4-methylpentan-2-yl)carbamate (31.2 mg, 0.081 mmol, 26% yield) as a colorless wax. LCMS (ESI) m/e 408.1 $[(\text{M}+\text{Na})^+]$, calcd $\text{C}_{18}\text{H}_{28}\text{BrNO}_3\text{Na}$, 408.1]; LC/MS retention time (method B): $t_R = 2.44$ min.

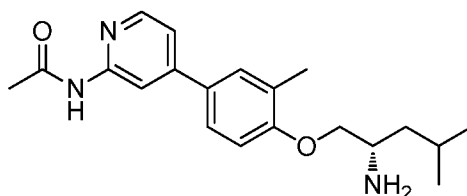
25



Part B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-methylphenoxy)-4-methylpentan-2-yl)carbamate

A mixture of sodium carbonate (0.061 mL, 0.121 mmol), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (0.028 g, 0.105 mmol),
 5 (*S*)-*tert*-butyl (1-(4-bromo-2-methylphenoxy)-4-methylpentan-2-yl)carbamate (0.0312 g, 0.081 mmol) in dioxane (1 mL) was purged with nitrogen 5 times. PdCl₂(dppf) (5.91 mg, 8.08 μmol) was added to the reaction mixture and the reaction was heated at 80 °C overnight. The reaction was cooled to room temperature and
 10 diluted with ethyl acetate. The organic layer was separated and washed with brine (1X). The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was used as it is at the next reaction. LCMS (ESI) *m/e* 442.3 [(M+H)⁺, calcd C₂₅H₃₆N₃O₄, 442.3]; LC/MS retention time (method B): *t*_R = 2.13 min.

15



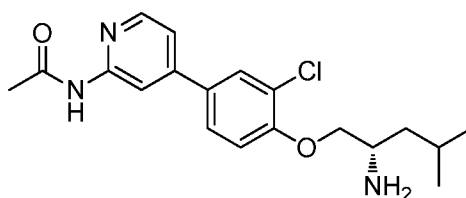
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)acetamide

A mixture of TFA (1 mL, 12.98 mmol) and (*S*)-*tert*-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-methylphenoxy)-4-methylpentan-2-yl)carbamate (35.8 mg,
 20 0.081 mmol) in CH₂Cl₂ (4 mL) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue was purified via reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate). To afford (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)acetamide (9.7 mg, 0.028
 25 mmol, 35% yield for two steps). ¹H NMR (500MHz, DMSO-d₆) δ 10.50 (s, 1H),

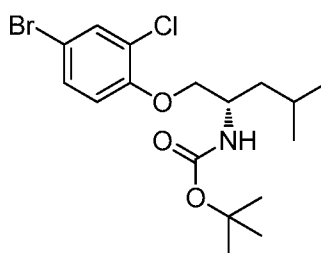
8.34 (br. s., 1H), 8.30 (d, $J=5.2$ Hz, 1H), 7.53 (br. s., 2H), 7.35 (d, $J=4.6$ Hz, 1H),
 7.08 - 7.03 (m, $J=9.2$ Hz, 1H), 3.92 - 3.86 (m, 1H), 3.84 - 3.78 (m, 1H), 3.10 (br. s.,
 1H), 2.26 (s, 3H), 2.12 (s, 3H), 1.87 - 1.79 (m, 1H), 1.40 - 1.31 (m, 1H), 1.27 (d,
 $J=6.4$ Hz, 1H), 0.93 (d, $J=6.7$ Hz, 3H), 0.89 (d, $J=6.4$ Hz, 3H); LCMS (ESI) m/e
 5 342.2 $[(M+H)^+]$, calcd $C_{20}H_{28}N_3O_2$, 342.2]; LC/MS retention time (method B): t_R =
 1.73 min.

Example 8

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)acetamide

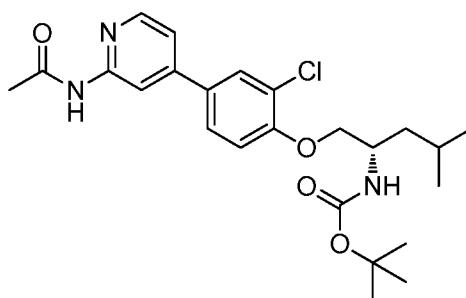


10



Part A: (S)-tert-butyl (1-(4-bromo-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate

Prepared as described in Example 1, Part 2A. ^1H NMR (400MHz,
 15 CHLOROFORM- d) δ 7.52 (d, $J=2.5$ Hz, 1H), 7.33 (dd, $J=8.8, 2.5$ Hz, 1H), 6.82 (d,
 $J=8.8$ Hz, 1H), 4.08 - 3.95 (m, 3H), 1.77 - 1.66 (m, 1H), 1.57 (br. m, 2H), 1.47 (s,
 9H), 0.98 (dd, $J=6.5, 3.8$ Hz, 6H). LCMS (ESI) m/e 428.0 $[(M+Na)^+]$, calcd
 $C_{17}H_{25}BrClNO_3Na$, 428.1]; LC/MS retention time (method B): t_R = 2.47 min.

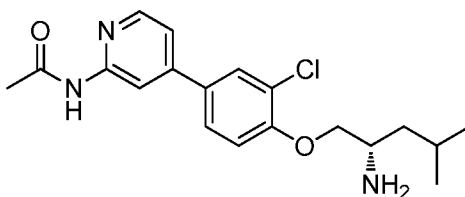


20

Part B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate

The mixture of sodium carbonate (0.113 mL, 0.226 mmol), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (0.051 g, 0.196 mmol),
 5 (S)-tert-butyl (1-(4-bromo-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate (0.0612 g, 0.150 mmol) in dioxane (1 mL) was evacuated and back-filled with N₂ (5X). PdCl₂(dppf) (0.011 g, 0.015 mmol) was added to the reaction mixture and the reaction was heated at 80 °C overnight. The reaction was diluted with ethyl acetate and washed with brine (1X). The ethyl acetate layer was separated, dried (Na₂SO₄),
 10 filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography (50% ethyl acetate in hexanes) to afford. (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate (51.7mg, 0.112 mmol, 74% yield). LCMS (ESI) *m/e* 462.2 [(M+H)⁺, calcd C₂₄H₃₃ClN₃O₄, 462.2]; LC/MS retention time (method B): *t*_R = 2.21 min.

15



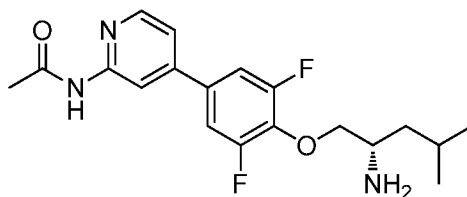
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)acetamide

A mixture of (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate (51.7 mg, 0.112 mmol) and TFA (1
 20 mL, 12.98 mmol) was stirred in CH₂Cl₂ (3 mL) at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was purified via reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate). (42.7 mg, 0.111 mmol, 99% yield). ¹H NMR (500MHz, DMSO-d₆) δ 10.58 (br. s., 1H), 8.35 (d, *J*=4.6 Hz, 2H), 7.81 (s, 1H), 7.70 (d, *J*=8.9 Hz, 1H), 7.42 (d, *J*=5.2 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 1H), 4.18 - 4.12 (m, 1H), 4.08 - 4.01 (m, 1H), 3.39 - 3.35 (m, 1H), 2.13 (s, 3H), 1.86 - 1.74 (m, 1H), 1.50 (d, *J*=6.1 Hz, 1H), 1.45 - 1.36 (m, 1H), 0.92 (dd, *J*=10.2, 6.6 Hz, 6H); LCMS (ESI) *m/e* 362.2 [(M+H)⁺, calcd C₁₉H₂₅ClN₃O₃, 362.2]; LC/MS retention time (method B): *t*_R = 1.69 min.

30

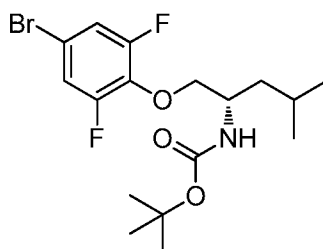
Example 9

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide



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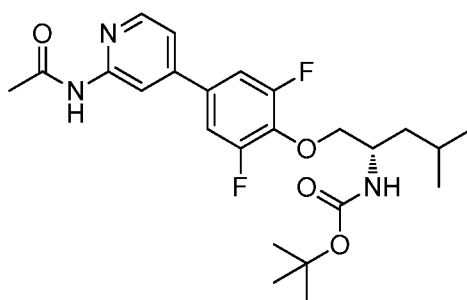
Prepared as described in Example 1.



Part A: (*S*)-tert-butyl (1-(4-bromo-2,6-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 - 7.33 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.78 - 4.61 (m, 1H), 4.09 - 3.90 (m, 3H), 1.68 (dq, *J* = 13.3, 6.7 Hz, 1H), 1.51 (t, *J* = 6.8 Hz, 2H), 1.45 (s, 9H), 0.95 (dd, *J* = 6.6, 5.4 Hz, 6H); LCMS (ESI) *m/e* 478.1 [(*M*+Na)⁺, calcd C₁₈H₂₅BrF₃N₁Na₁O₄, 478.0]; LC/MS retention time (method B): *t*_R = 2.45 min.

15



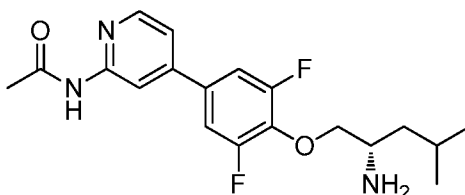
Part B: (*S*)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2,6-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 8.42 (s, 1H), 8.28 (d, *J* = 5.3 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.15 (dd, *J* = 5.4, 1.7 Hz, 1H), 4.88 (d, *J* = 9.0

20

Hz, 1H), 4.24 - 4.13 (m, 2H), 3.94 (s, 1H), 2.24 (s, 3H), 1.74 (dt, $J = 13.5, 6.7$ Hz, 1H), 1.55 (t, $J = 7.3$ Hz, 2H), 1.24 (s, 9H), 0.97 (d, $J = 6.5$ Hz, 6H); ^{19}F NMR (376 MHz, Chloroform- d) δ -126.89; LCMS (ESI) m/e 464.2 $[(M+H)^+]$, calcd $\text{C}_{24}\text{H}_{32}\text{F}_2\text{N}_3\text{O}_4$, 464.2]; LC/MS retention time (method A): $t_R = 2.24$ min.

5

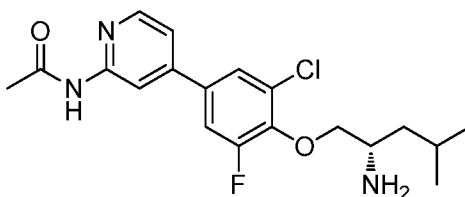


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide.

Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide (48.4 mg, 0.152 mmol, 99% yield for final step) as an off-white foam. ^1H NMR (500 MHz, DMSO- d_6) δ 10.62 (s, 1H), 8.37 (d, $J = 5.3$ Hz, 1H), 8.32 (s, 1H), 7.59 - 7.48 (m, 2H), 7.42 (dd, $J = 5.2, 1.8$ Hz, 1H), 4.16 (dd, $J = 10.0, 4.5$ Hz, 1H), 4.07 (dd, $J = 9.9, 5.7$ Hz, 1H), 3.24 (dq, $J = 10.5, 5.8$ Hz, 1H), 2.13 (s, 3H), 1.82 - 1.74 (m, 1H), 1.46 (ddd, $J = 13.7, 8.1, 5.8$ Hz, 1H), 1.35 (ddd, $J = 13.9, 8.1, 6.3$ Hz, 1H), 0.90 (dd, $J = 9.0, 6.5$ Hz, 6H); LCMS (ESI) m/e 364.1 $[(M+H)^+]$, calcd $\text{C}_{19}\text{H}_{24}\text{F}_2\text{N}_3\text{O}_2$, 364.2]; LC/MS retention time (method A): $t_R = 1.81$ min.

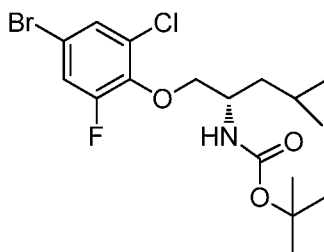
Example 10

(S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide



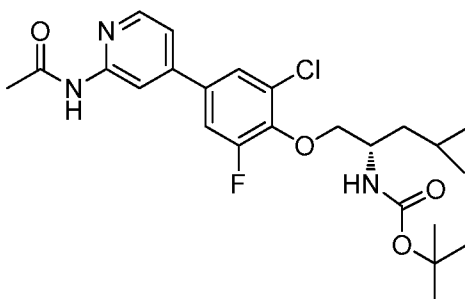
Prepared as described in Example 1.

25



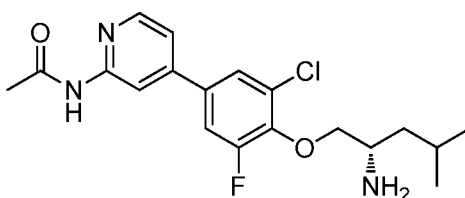
Part A: (*S*)-tert-butyl (1-(4-bromo-2,6-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

LCMS (ESI) m/e 424.2 $[(M+H)^+]$, calcd $C_{17}H_{25}BrClF_2N_1O_3$, 424.1]; LC/MS
5 retention time (method A): t_R = 2.37 min.



Part B: (*S*)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-chloro-6-fluorophenoxy)-4-methylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 480.2 $[(M+H)^+]$, calcd $C_{24}H_{32}F_2N_3O_4$, 480.2]; LC/MS
retention time (method B): t_R = 2.28 min.



Part C: (*S*)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide.
15

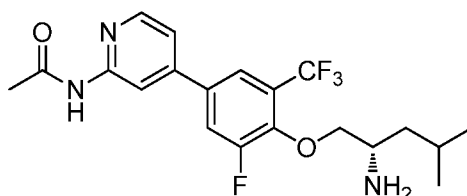
Obtained (*S*)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide (26.5 mg, 0.066 mmol, 56% yield for final step) as a colorless solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.60 (s, 1H), 8.37 (d, J = 5.2 Hz, 1H), 8.30 (s, 1H), 7.67 (d, J = 9.5 Hz, 2H), 7.43 (d, J = 5.1 Hz, 1H), 4.04 (dd, J = 9.4, 4.7 Hz, 1H), 3.96 (dd, J = 9.5, 6.2 Hz, 1H), 3.11 (dq, J = 10.7, 5.1 Hz, 1H),
20 2.12 (s, 3H), 1.79 (dq, J = 13.6, 6.4 Hz, 1H), 1.41 (ddd, J = 13.6, 8.5, 5.2 Hz, 1H),

1.26 (ddd, $J = 14.1, 8.6, 5.8$ Hz, 1H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.88 (d, $J = 6.5$ Hz, 3H); LCMS (ESI) m/e 380.2 $[(M+H)^+]$, calcd $C_{19}H_{24}ClF_1N_3O_2$, 380.2]; LC/MS retention time (method B): $t_R = 1.82$ min.

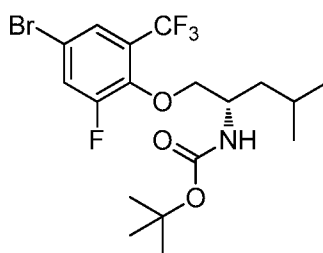
5

Example 11

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluoro-5-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide



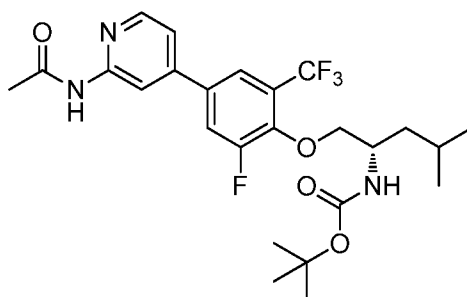
10 Prepared as described in Example 1.



Part A: (S)-tert-butyl (1-(4-bromo-2-fluoro-6-(trifluoromethyl)phenoxy)-4-methylpentan-2-yl)carbamate.

15 ^1H NMR (400 MHz, Chloroform- d) δ 7.52 (t, $J = 1.9$ Hz, 1H), 7.47 (dd, $J = 10.7, 2.4$ Hz, 1H), 4.76 (d, $J = 9.1$ Hz, 1H), 4.19 (s, 2H), 3.96 (d, $J = 7.7$ Hz, 1H), 1.74 (dq, $J = 13.5, 6.7$ Hz, 1H), 1.54 (t, $J = 7.1$ Hz, 2H), 1.47 (s, 9H), 0.98 (d, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e 480.0 $[(M+Na)^+]$, calcd $C_{18}H_{24}BrF_4N_1Na_1O_3$, 480.1]; LC/MS retention time (method B): $t_R = 2.50$ min.

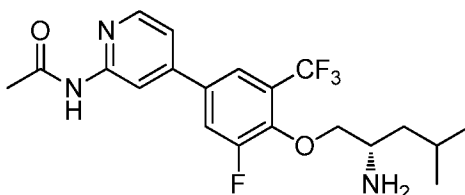
20



Part B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-fluoro-6-(trifluoromethyl)phenoxy)-4-methylpentan-2-yl)carbamate.

LCMS (ESI) m/e 536.2 $[(M+Na)^+]$, calcd $C_{25}H_{31}F_4Na_1N_3O_4$, 536.2]; LC/MS retention time (method B): t_R = 2.34 min.

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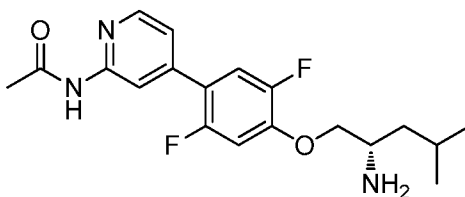
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluoro-5-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide.

10 Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluoro-5-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide (49 mg, 0.116 mmol, 75% yield for final step) as a colorless solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.63 (s, 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.35 (s, 1H), 8.01 (dd, J = 12.9, 2.2 Hz, 1H), 7.74 (s, 1H), 7.48 (d, J = 5.4 Hz, 1H), 4.06 (p, J = 8.2 Hz, 2H), 3.12 - 3.03 (m, 1H), 2.13 (s, 3H), 1.82 (dt, J = 13.6, 7.2 Hz, 1H), 1.35 (ddd, J = 13.4, 8.9, 4.8 Hz, 1H), 1.22 (ddd, J = 13.8, 9.0, 5.5 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); LCMS (ESI) m/e 414.2 $[(M+H)^+]$, calcd $C_{20}H_{24}F_4N_3O_2$, 414.2]; LC/MS retention time (method A): t_R = 2.01 min.

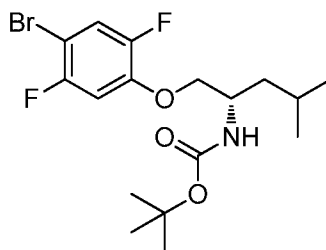
20

Example 12

(S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide

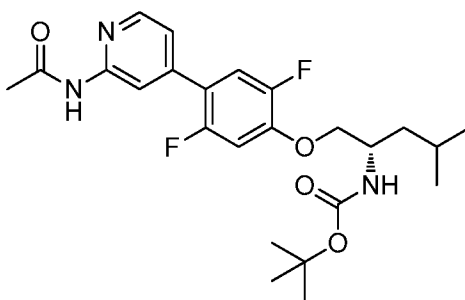


25 Prepared as described in Example 1.



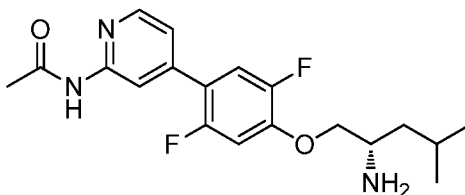
Part A: (S)-tert-butyl (1-(4-bromo-2,5-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 7.29 (t, J = 9.5 Hz, 1H), 6.81 (dd, J = 9.5, 7.3 Hz, 1H), 4.68 (s, 1H), 4.09 - 3.91 (m, 3H), 1.71 (dt, J = 13.4, 7.0 Hz, 1H), 1.53 (dd, J = 15.3, 7.8 Hz, 2H), 1.47 (s, 9H), 0.97 (dd, J = 6.6, 4.5 Hz, 6H); LCMS (ESI) m/e 408.0 [(M+H)⁺, calcd C₁₇H₂₅BrF₂N₁O₃, 408.1]; LC/MS retention time (method A): t_R = 2.40 min.



Part B: (S)-tert-butyl (1-(4-(2-acetamidopyridin-4-yl)-2,5-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

LCMS (ESI) m/e 464.2 [(M+H)⁺, calcd C₂₄H₃₂F₂N₃O₄, 464.3]; LC/MS retention time (method A): t_R = 2.29 min.



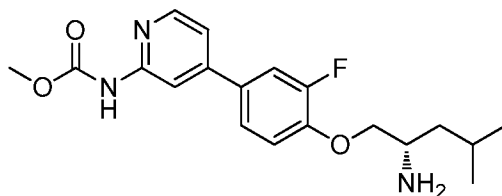
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide.

Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide (46.4 mg, 0.125 mmol, 77% yield for final step) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 10.59 (s, 1H), 8.37 (d, J

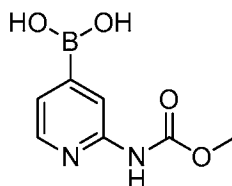
= 5.2 Hz, 1H), 8.29 (s, 1H), 7.54 (dd, $J = 11.8, 7.3$ Hz, 1H), 7.34 (dd, $J = 12.3, 7.2$ Hz, 1H), 7.26 (d, $J = 5.2$ Hz, 1H), 4.08 (dd, $J = 9.8, 4.5$ Hz, 1H), 3.98 (dd, $J = 10.0, 6.4$ Hz, 1H), 3.24 (p, $J = 6.0$ Hz, 1H), 2.11 (s, 3H), 1.80 (dq, $J = 15.3, 8.4, 7.6$ Hz, 1H), 1.35 (qt, $J = 13.7, 6.8$ Hz, 2H), 0.91 (dd, $J = 14.1, 6.6$ Hz, 6H); LCMS (ESI) m/e 364.2 $[(M+H)^+]$, calcd $C_{19}H_{24}F_2N_3O_2$, 364.2]; LC/MS retention time (method A): $t_R = 1.82$ min.

Example 13

(*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate



Prepared as described in Example 1.

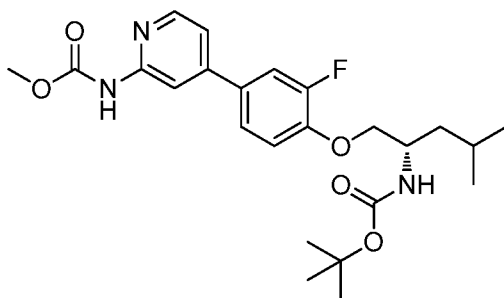


Part A: (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid

The mixture of 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (0.079 g, 0.166 mmol), potassium acetate (2.446 g, 24.92 mmol), 2nd generation Xphos precatalyst (0.065 g, 0.083 mmol), methyl (4-chloropyridin-2-yl)carbamate (1.55 g, 8.31 mmol) and hypodiboric acid (1.117 g, 12.46 mmol) in ethanol (80 mL) was degassed three times via vacuum/ N_2 fill cycle. The reaction mixture was heated at 80 °C for 3 h. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure and the solid was washed with acetone. The remaining solid was suspended with mixture of methanol and CH_2Cl_2 . The suspension was filtered and the filtrate was concentrated under reduced pressure to give the crude product as a solid. The solid was suspended in water and filtered. The

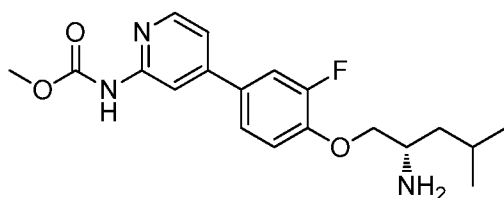
solid was washed with acetone to give (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (702mg, 3.58 mmol, 43% yield) as an off-white solid. LCMS (ESI) m/e 197.2 $[(M+H)^+]$, calcd $C_7H_{10}BN_2O_4$, 197.1]; LC/MS retention time (method B): t_R = 0.46 min.

5



Part B: (S)-tert-butyl (1-(4-(2-aminopyridin-4-yl)-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate.

^1H NMR (400 MHz, Chloroform- d) δ 9.86 (s, 1H), 8.35 (d, J = 5.4 Hz, 1H),
 10 8.31 - 8.24 (m, 1H), 7.52 - 7.39 (m, 2H), 7.17 (dd, J = 5.4, 1.7 Hz, 1H), 7.06 (t, J =
 8.6 Hz, 1H), 4.84 (d, J = 8.5 Hz, 1H), 4.15 - 3.99 (m, 3H), 3.87 (s, 3H), 1.80 - 1.67
 (m, 1H), 1.56 (dt, J = 13.3, 7.8 Hz, 2H), 1.47 (s, 9H), 0.99 (d, J = 3.7 Hz, 3H), 0.97
 (d, J = 3.6 Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -133.39; LCMS (ESI) m/e
 462.2 $[(M+H)^+]$, calcd $C_{24}H_{33}F_1N_3O_5$, 462.2]; LC/MS retention time (method B): t_R =
 15 2.20 min.



Part C: (S)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate.

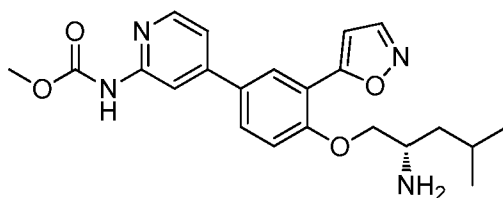
20 Obtained (S)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-
 fluorophenyl)pyridin-2-yl)carbamate (33.2 mg, 0.091 mmol, 93% yield for the final
 step) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.26 (s, 1H), 8.30 (d,
 J = 5.3 Hz, 1H), 8.09 (s, 1H), 7.63 (dd, J = 12.7, 2.4 Hz, 1H), 7.55 - 7.49 (m, 1H),
 7.37 (dd, J = 5.3, 1.9 Hz, 1H), 7.32 (t, J = 8.7 Hz, 1H), 3.97 (dd, J = 9.4, 5.0 Hz,
 25 1H), 3.90 (dd, J = 9.4, 6.5 Hz, 1H), 3.71 (s, 3H), 3.12 (p, J = 5.6 Hz, 1H), 1.83 (dt, J

= 14.1, 6.7 Hz, 1H), 1.33 (ddd, $J = 13.4, 8.5, 4.9$ Hz, 1H), 1.26 (ddd, $J = 13.9, 8.7, 5.5$ Hz, 1H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.89 (d, $J = 6.5$ Hz, 3H); LCMS (ESI) m/e 362.1 $[(M+H)^+]$, calcd $C_{19}H_{25}F_1N_3O_3$, 362.2]; LC/MS retention time (method A): $t_R = 1.85$ min.

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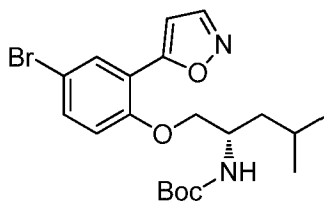
Example 14

(*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate



10

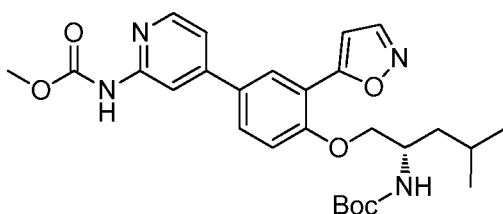
Prepared as described in Example 1.



15 *Part A: (S)-tert-butyl (1-(4-bromo-2-(isoxazol-5-yl)phenoxy)-4-methylpentan-2-yl)carbamate.*

^1H NMR (400 MHz, Chloroform- d) δ 8.31 (s, 1H), 8.09 (d, $J = 2.4$ Hz, 1H), 7.46 (dd, $J = 9.1, 2.6$ Hz, 1H), 6.88 (d, $J = 9.0$ Hz, 2H), 4.60 (d, $J = 8.9$ Hz, 1H), 4.19 (d, $J = 7.0$ Hz, 1H), 4.02 (qd, $J = 9.2, 5.2$ Hz, 2H), 1.75 (dq, $J = 13.6, 6.7$ Hz, 1H), 1.46 (d, $J = 12.0$ Hz, 11H), 0.98 (d, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e 461.0 $[(M+Na)^+]$, calcd $C_{20}H_{27}Br_1N_2Na_1O_4$, 461.1]; LC/MS retention time (method B): $t_R = 2.41$ min.

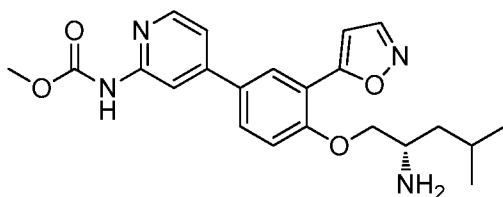
20



Part B: (S)-methyl (4-(4-((2-Boc-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate.

LCMS (ESI) m/e 511.4 $[(M+H)^+]$, calcd $C_{27}H_{35}N_4O_6$, 511.2]; LC/MS retention time (method A): t_R = 2.27 min.

5



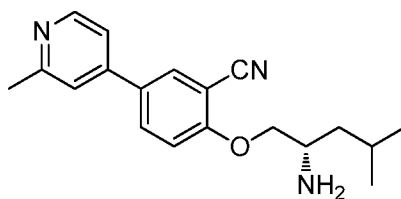
Part C: (S)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate.

Obtained (S)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate (10.9 mg, 0.027 mmol, 34% yield for the final
 10 step) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.74 (d, J = 1.7 Hz, 1H), 8.34 (d, J = 5.2 Hz, 1H), 8.19 (t, J = 2.4 Hz, 2H), 7.89 (dd, J = 8.7, 2.4 Hz, 1H), 7.44 (d, J = 5.3 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 4.18 (dd, J = 9.7, 4.5 Hz, 1H), 4.09 (dd, J = 9.6, 6.3 Hz, 1H), 3.72 (s, 3H), 3.36 (d, J = 4.3 Hz,
 15 1H), 1.83 (dt, J = 13.7, 6.7 Hz, 1H), 1.44 (dt, J = 13.6, 7.0 Hz, 1H), 1.41 - 1.32 (m, 1H), 0.92 (dd, J = 9.4, 6.6 Hz, 6H); LCMS (ESI) m/e 411.1 $[(M+H)^+]$, calcd $C_{22}H_{27}N_4O_4$, 411.2]; LC/MS retention time (method B): t_R = 1.63 min.

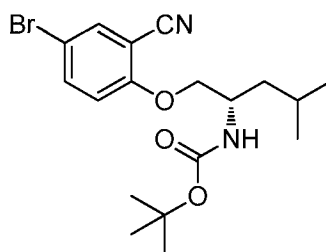
Example 15

20 (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile

Prepared as described in Example 1.

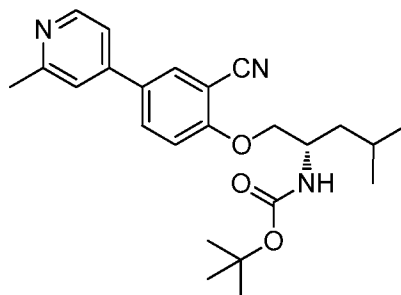


25



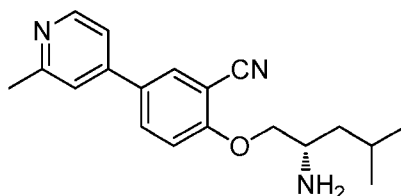
Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 7.68 (d, J = 2.5 Hz, 1H), 7.64 (dd, J = 8.9, 2.5 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 4.71 (s, 1H), 4.12 (t, J = 6.1 Hz, 1H), 4.10 - 3.98 (m, 2H), 1.79 - 1.67 (m, 1H), 1.59 (dd, J = 13.8, 6.9 Hz, 2H), 1.47 (s, 9H), 0.98 (dd, J = 6.5, 5.2 Hz, 6H); LCMS (ESI) m/e 397.1 [(M+H)⁺, calcd C₁₈H₂₆BrN₂O₃, 397.1]; LC/MS retention time (method A): t_R = 2.22 min.



Part B: (S)-tert-butyl (1-(2-cyano-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 8.56 (d, J = 5.3 Hz, 1H), 7.84 (d, J = 2.3 Hz, 1H), 7.80 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 (d, J = 1.7 Hz, 1H), 7.25 (dd, J = 5.3, 1.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 4.81 (d, J = 8.6 Hz, 1H), 4.21 - 4.11 (m, 2H), 4.10 - 4.03 (m, 1H), 2.64 (s, 3H), 1.76 - 1.68 (m, 1H), 1.60 (tt, J = 15.6, 6.2 Hz, 2H), 1.46 (s, 9H), 0.98 (dd, J = 6.5, 5.0 Hz, 6H); LCMS (ESI) m/e 410.2 [(M+H)⁺, calcd C₂₄H₃₂N₃O₃, 410.2]; LC/MS retention time (method A): t_R = 2.18 min.



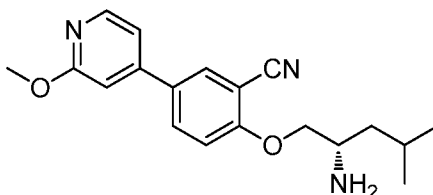
Part C: (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile.

Obtained (48.4 mg, 0.152 mmol, 99% yield for the final step) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.49 (d, *J* = 5.3 Hz, 1H), 8.24 (d, *J* = 2.4 Hz, 1H), 8.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.65 (s, 1H), 7.57 - 7.52 (m, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 4.09 (dd, *J* = 9.5, 5.1 Hz, 1H), 4.01 (dd, *J* = 9.5, 6.2 Hz, 1H), 3.16 (dq, *J* = 10.8, 5.4 Hz, 1H), 2.53 (s, 3H), 2.51 (s, 2H), 1.83 (dq, *J* = 12.8, 6.5 Hz, 1H), 1.39 (ddd, *J* = 13.5, 8.4, 5.1 Hz, 1H), 1.30 (ddd, *J* = 13.8, 8.6, 5.9 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 310.1 [(M+H)⁺, calcd C₁₉H₂₄N₃O₁, 310.2]; LC/MS retention time (method A): *t*_R = 1.82 min.

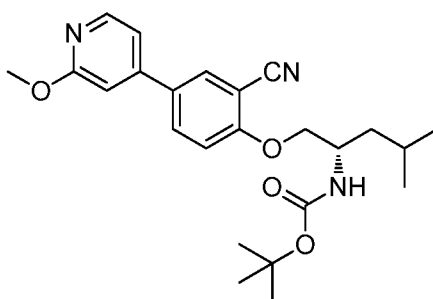
10

Example 16

(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methoxypyridin-4-yl)benzonitrile



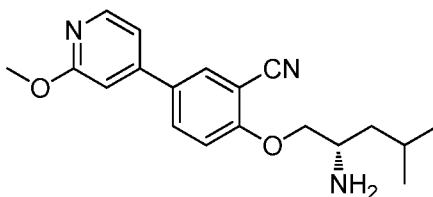
15 Prepared as described in Example 1.



Part A: (*S*)-tert-butyl (1-(2-cyano-4-(2-methylpyridin-4-yl)phenoxy)-4-methoxypentan-2-yl)carbamate.

20 ¹H NMR (500 MHz, Chloroform-d) δ 8.20 (dd, *J* = 5.4, 0.7 Hz, 1H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.11 - 7.05 (m, 1H), 7.00 (dd, *J* = 5.4, 1.6 Hz, 1H), 6.85 (dd, *J* = 1.6, 0.7 Hz, 1H), 4.84 (d, *J* = 8.7 Hz, 1H), 4.20 - 4.14 (m, 1H), 4.11 (ddd, *J* = 8.7, 4.6, 2.5 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.97 (s, 3H), 1.76 - 1.66 (m, 1H), 1.64 - 1.52 (m, 2H), 1.44 (s, 9H), 0.96 (dd, *J* = 6.6, 5.7 Hz, 6H); LCMS

(ESI) m/e 426.2 $[(M+H)^+]$, calcd $C_{24}H_{32}N_3O_4$, 426.2]; LC/MS retention time (method A): t_R = 2.27 min.



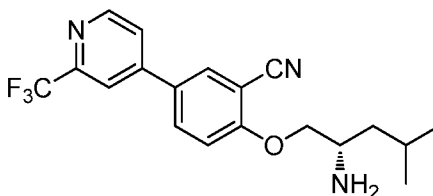
5 *Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methoxypyridin-4-yl)benzonitrile.*

Obtained (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methoxypyridin-4-yl)benzonitrile (28.6 mg, 0.088 mmol, 60% yield for the final step) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.23 (dd, J = 6.7, 3.9 Hz, 2H), 8.10 (dd, J = 8.9, 2.4 Hz, 1H), 7.41 - 7.32 (m, 2H), 7.18 (s, 1H), 4.05 (dd, J = 9.3, 5.1 Hz, 1H),
 10 3.98 (dd, J = 9.4, 6.3 Hz, 1H), 3.90 (s, 3H), 3.12 (dq, J = 10.4, 5.4 Hz, 1H), 1.83 (tt, J = 13.3, 6.7 Hz, 1H), 1.36 (ddd, J = 13.4, 8.5, 4.9 Hz, 1H), 1.26 (ddd, J = 13.9, 8.8, 5.7 Hz, 1H), 0.92 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H); LCMS (ESI) m/e 326.1 $[(M+H)^+]$, calcd $C_{19}H_{24}N_3O_2$, 326.2]; LC/MS retention time (method A): t_R = 1.88 min.

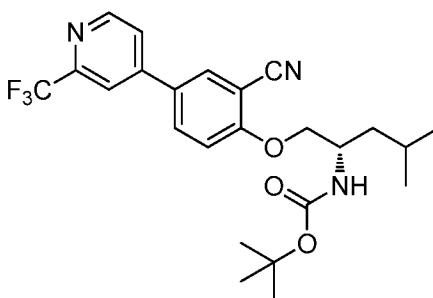
15

Example 17

(S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile



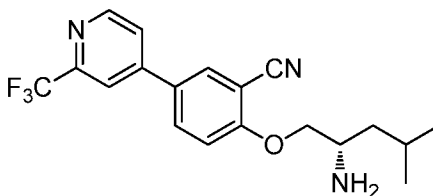
20 Prepared as described in Example 1.



Part A: (S)-tert-butyl (1-(2-cyano-4-(2-(trifluoromethyl)pyridin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 8.80 (d, J = 5.1 Hz, 1H), 7.89 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 - 7.80 (m, 1H), 7.64 (dd, J = 5.1, 1.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 4.79 (d, J = 8.5 Hz, 1H), 4.26 - 4.14 (m, 2H), 4.11 - 4.04 (m, 1H), 1.73 (p, J = 6.5 Hz, 1H), 1.66 - 1.54 (m, 2H), 1.46 (s, 9H), 0.98 (t, J = 6.3 Hz, 6H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -68.06; LCMS (ESI) m/e 486.2 [(M+Na)⁺, calcd C₂₄H₂₈F₃Na₁N₃O₃, 486.2]; LC/MS retention time (method B): t_R = 2.35 min.

10



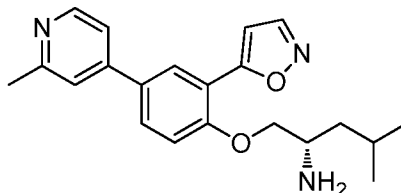
Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile.

Obtained (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile (34.3 mg, 0.093 mmol, 93% yield for the final step) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.81 (d, J = 5.2 Hz, 1H), 8.46 (d, J = 2.9 Hz, 1H), 8.34 - 8.21 (m, 2H), 8.11 (d, J = 5.1 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 4.08 (dd, J = 9.9, 5.2 Hz, 1H), 4.05 - 3.95 (m, 1H), 3.13 (d, J = 7.5 Hz, 1H), 1.85 (t, J = 7.0 Hz, 1H), 1.43 - 1.32 (m, 1H), 1.27 (q, J = 11.7, 9.8 Hz, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); LCMS (ESI) m/e 364.1 [(M+H)⁺, calcd C₁₉H₂₁F₃N₃O₁, 364.2]; LC/MS retention time (method B): t_R = 1.97 min.

20

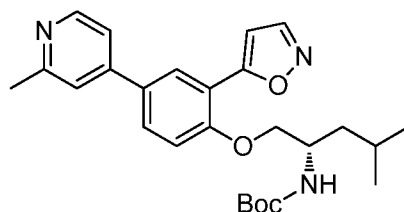
Example 18

(S)-1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-amine



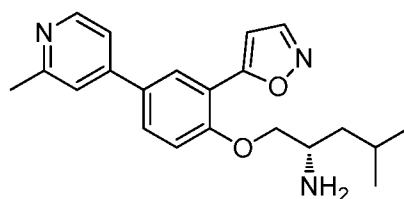
25

Prepared as described in Example 1.



Part A: (S)-tert-butyl (1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate.

LCMS (ESI) m/e 452.1 $[(M+H)^+]$, calcd $C_{26}H_{34}N_3O_4$, 452.2]; LC/MS retention time (method B): t_R = 2.03 min.

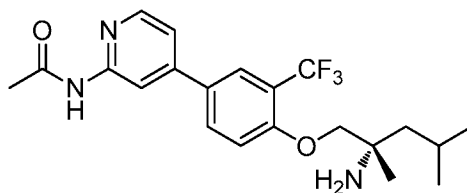


Part B: (S)-1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-amine.

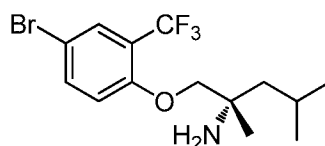
Obtained (S)-1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-amine (14.6 mg, 0.041 mmol, 49% yield for the final step) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.72 (d, J = 1.9 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.8, 2.4 Hz, 1H), 7.65 (s, 1H), 7.59 - 7.52 (m, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 1.9 Hz, 1H), 4.12 (dd, J = 9.6, 4.6 Hz, 1H), 4.04 (dd, J = 9.5, 6.3 Hz, 1H), 3.27 (dq, J = 10.3, 5.3 Hz, 1H), 2.51 (s, 3H), 1.83 (dt, J = 14.0, 6.7 Hz, 1H), 1.40 (ddd, J = 13.4, 8.4, 5.2 Hz, 1H), 1.32 (ddd, J = 13.7, 8.5, 5.7 Hz, 1H), 0.91 (dd, J = 10.5, 6.5 Hz, 6H); LCMS (ESI) m/e 352.1 $[(M+H)^+]$, calcd $C_{21}H_{26}N_3O_2$, 352.2]; LC/MS retention time (method B): t_R = 1.50 min.

Example 19

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

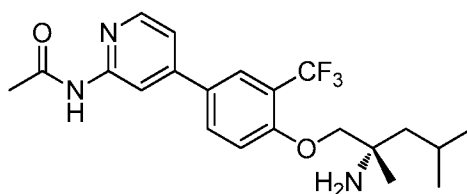


5



Part A: (S)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

To a 50 mL round-bottomed flask was added (*S*)-2-amino-2,4-dimethylpentan-1-ol (66.1 mg, 0.504 mmol) in tetrahydrofuran (1.5 mL) to give a colorless solution. Potassium *tert*-butoxide (0.604 mL, 0.604 mmol) (1.0 M in THF) was added dropwise under nitrogen. After 5 min, 4-bromo-1-fluoro-2-(trifluoromethyl)benzene (0.079 mL, 0.604 mmol) was added in one portion. The mixture was stirred at rt for 2h. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to obtain crude (*S*)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (146 mg, 0.412 mmol, 82% yield) as a tan oil which was used as is. ¹H NMR (500 MHz, Chloroform-d) δ 7.70 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.80 - 3.72 (m, 2H), 1.83 - 1.73 (m, 1H), 1.53 - 1.44 (m, 2H), 1.23 (s, 3H), 0.98 (dd, *J* = 12.2, 6.7 Hz, 6H); ¹⁹F NMR (470 MHz, Chloroform-d) δ -62.61.; LCMS (ESI) *m/e* 354.0 [(*M*+H)⁺, calcd C₁₄H₂₀BrF₃N₁O₁, 354.1]; LC/MS retention time (method B): *t*_R = 2.14 min.

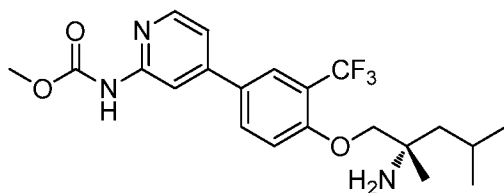


Part B: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

To a 2 mL vial was added (S)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (43.5 mg, 0.123 mmol), *N*-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)acetamide (26.5 mg, 0.147 mmol) (prepared as described in Example 1, Part A), and Na₂CO₃ (0.184 mL, 0.368 mmol) in dioxane (0.5 mL) under nitrogen to give a colorless suspension. 1,1'-bis(diphenylphosphino)ferrocene palladium(II) dichloride, toluene (5.05 mg, 6.14 μmol) was added under nitrogen. The vial was sealed and heated at 130 °C (microwave) for 2 h (100 °C oil heating for 2 h was fine and was used for all other examples). The mixture was cooled to rt and diluted with EtOAc then passed through a plug of Na₂SO₄. The organic solution was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (acetonitrile: water with 10 mM ammonium) to give (S)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide (24 mg, 0.057 mmol, 47% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 10.58 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 2H), 7.97 (t, *J* = 8.1 Hz, 1H), 7.89 (s, 1H), 7.44 (d, *J* = 5.4 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 3.86 (q, *J* = 8.8 Hz, 2H), 2.13 (s, 3H), 1.79 (dq, *J* = 10.2, 5.2, 4.0 Hz, 1H), 1.39 (d, *J* = 5.5 Hz, 2H), 1.12 (s, 3H), 0.91 (d, *J* = 6.6 Hz, 6H); LCMS (ESI) *m/e* 410.2 [(M-H)⁻, calcd C₂₀H₂₃F₃N₃O₂, 410.2]; LC/MS retention time (method B): *t*_R = 1.87 min.

Example 20

(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)carbamate



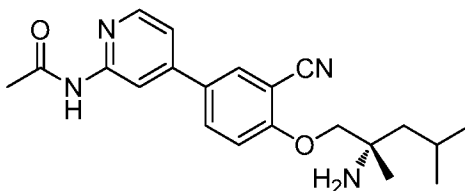
Prepared as described in Example 19 to obtain (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)carbamate (22.9 mg, 0.051 mmol, 38% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 10.29 (s, 1H), 8.32 (d, *J* = 5.3 Hz, 1H), 8.11 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.90

(s, 1H), 7.39 (dd, $J = 12.5, 7.0$ Hz, 2H), 3.87 (q, $J = 8.8$ Hz, 2H), 3.71 (s, 3H), 1.79 (dq, $J = 10.8, 5.6, 4.8$ Hz, 1H), 1.40 (d, $J = 5.6$ Hz, 2H), 1.13 (s, 3H), 0.91 (d, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e 426.3 [(M-H)⁺, calcd C₂₁H₂₇F₃N₃O₃, 426.2]; LC/MS retention time (method A): $t_R = 2.23$ min.

5

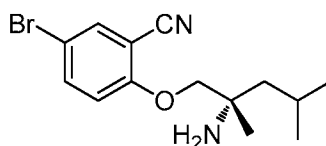
Example 21

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide



10

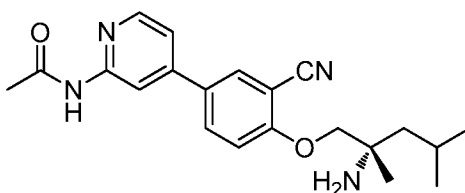
Prepared as described in Example 19



Part A: (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-bromobenzonitrile.

15 ¹H NMR (400 MHz, Chloroform-d) δ 7.68 (d, $J = 2.5$ Hz, 1H), 7.63 (dd, $J = 8.9, 2.4$ Hz, 1H), 6.86 (d, $J = 9.0$ Hz, 1H), 3.84 - 3.77 (m, 2H), 1.87 - 1.74 (m, 1H), 1.59 - 1.53 (m, 2H), 1.27 (s, 3H), 1.00 (dd, $J = 8.3, 6.6$ Hz, 6H); LCMS (ESI) m/e 311.1, 313.1 Br pattern [(M+H)⁺, calcd C₁₄H₂₀BrN₂O, 311.1]; LC/MS retention time (method A): $t_R = 2.01$ min.

20



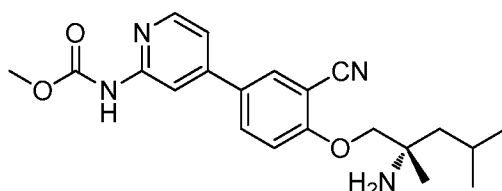
Part B: (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide.

25 Obtained (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide (28.9 mg, 0.078 mmol, 70% yield) as an off-

white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.58 (s, 1H), 8.44 - 8.29 (m, 2H), 8.12 (s, 1H), 8.00 (d, $J = 8.9$ Hz, 1H), 7.44 (d, $J = 5.3$ Hz, 1H), 7.39 (d, $J = 8.8$ Hz, 1H), 3.91 (t, $J = 6.7$ Hz, 2H), 2.13 (s, 3H), 1.82 (p, $J = 6.2$ Hz, 1H), 1.43 (t, $J = 5.4$ Hz, 2H), 1.15 (s, 3H), 0.93 (dd, $J = 6.7, 3.7$ Hz, 6H); LCMS (ESI) m/e 367.3 $[(M+H)^+]$, calcd $\text{C}_{21}\text{H}_{27}\text{N}_4\text{O}_2$, 367.2]; LC/MS retention time (method A): $t_R = 1.82$ min.

Example 22

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)carbamate



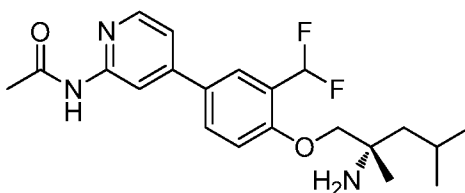
10

Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)carbamate (21.1 mg, 0.053 mmol, 47% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.29 (s, 1H), 8.32 (d, $J = 5.3$ Hz, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 8.01 (d, $J = 9.1$ Hz, 1H), 7.40 (dd, $J = 11.9, 7.1$ Hz, 2H), 3.91 (t, $J = 6.5$ Hz, 2H), 3.71 (s, 3H), 1.81 (dq, $J = 12.5, 6.2$ Hz, 1H), 1.42 (q, $J = 8.2, 6.6$ Hz, 2H), 1.15 (s, 3H), 0.93 (dd, $J = 6.8, 3.8$ Hz, 6H); LCMS (ESI) m/e 405.2 $[(M+Na)^+]$, calcd $\text{C}_{21}\text{H}_{26}\text{N}_4\text{NaO}_3$, 405.2]; LC/MS retention time (method B): $t_R = 1.87$ min.

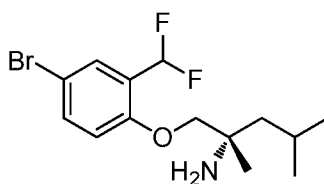
20

Example 23

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)acetamide

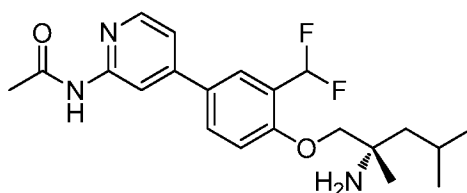


25 Prepared as described in Example 19.



Part A: *(S)*-1-(4-bromo-2-(difluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine.

^1H NMR (400 MHz, Chloroform- d) δ 7.67 (dd, J = 2.4, 1.1 Hz, 1H), 7.53 (ddt, J = 8.8, 2.3, 1.1 Hz, 1H), 6.93 - 6.70 (m, 2H), 3.79 - 3.72 (m, 2H), 1.85 - 1.73 (m, 1H), 1.52 - 1.47 (m, 2H), 1.23 (s, 3H), 0.99 (dd, J = 7.6, 6.6 Hz, 6H); ^{19}F NMR (376 MHz, Chloroform- d) δ -116.21; LCMS (ESI) m/e 336.1 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{14}\text{H}_{21}\text{BrF}_2\text{N}_1\text{O}_1$, 336.1]; LC/MS retention time (method A): t_R = 2.18 min.



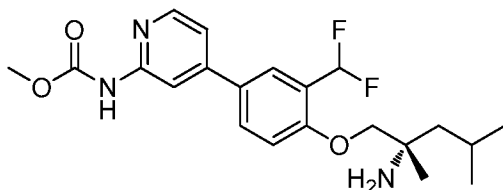
Part B: *(S)*-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)acetamide.

Obtained *(S)*-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)acetamide (13 mg, 0.033 mmol, 32% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.56 (s, 1H), 8.45 - 8.29 (m, 2H), 7.87 (d, J = 8.7 Hz, 1H), 7.82 (s, 1H), 7.49 - 7.12 (m, 3H), 3.84 (s, 2H), 2.13 (s, 3H), 1.79 (dt, J = 14.1, 7.3 Hz, 1H), 1.47 - 1.34 (m, 2H), 1.14 (s, 3H), 0.92 (dd, J = 11.3, 6.6 Hz, 6H); LCMS (ESI) m/e 392.3 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{21}\text{H}_{28}\text{F}_2\text{N}_3\text{O}_2$, 392.2]; LC/MS retention time (method A): t_R = 1.90 min.

20

Example 24

(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)carbamate

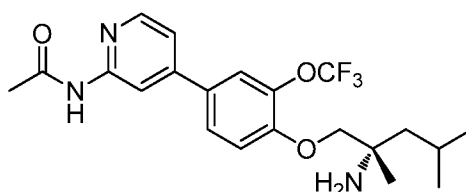


Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)carbamate (15.4 mg, 0.037 mmol, 35% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.26 (s, 1H), 8.31 (d, *J* = 5.3 Hz, 1H), 8.11 (s, 1H), 7.91 - 7.85 (m, 1H), 7.83 (s, 1H), 7.42 - 7.13 (m, 3H), 3.84 (s, 2H), 3.70 (s, 3H), 1.79 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.41 (qd, *J* = 14.0, 5.6 Hz, 2H), 1.14 (s, 3H), 0.92 (dd, *J* = 11.4, 6.6 Hz, 6H); LCMS (ESI) *m/e* 408.3 [(*M*+*H*)⁺, calcd C₂₁H₂₈F₂N₃O₃, 408.2]; LC/MS retention time (method A): *t*_R = 2.00 min.

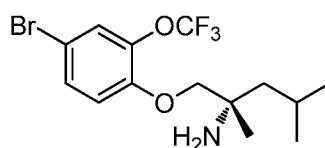
10

Example 25

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide



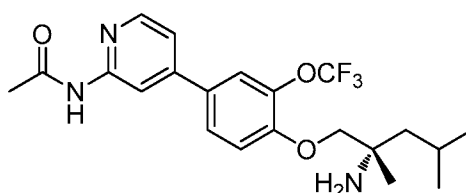
15 Prepared as described in Example 19.



Part A: (S)-1-(4-bromo-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine.

¹H NMR (400 MHz, Chloroform-*d*) δ 7.41 - 7.34 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 3.76 - 3.72 (m, 2H), 1.83 - 1.76 (m, 1H), 1.49 - 1.47 (m, 2H), 1.23 (s, 3H), 1.01 - 0.98 (m, 6H); ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -58.22; LCMS (ESI) *m/e* 370.1 [(*M*+*H*)⁺, calcd C₁₄H₂₀BrF₃N₁O₂, 370.1]; LC/MS retention time (method A): *t*_R = 2.33 min.

25

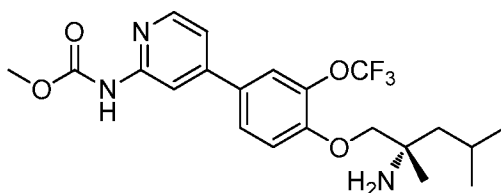


Part B: (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide.

Obtained (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide (14.1 mg, 0.032 mmol, 36% yield) as an off-white as solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 8.35 (d, *J* = 4.6 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 7.41 (d, *J* = 5.1 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 3.83 (t, *J* = 7.3 Hz, 2H), 2.12 (s, 3H), 1.81 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.39 (q, *J* = 7.6, 6.3 Hz, 2H), 1.13 (s, 3H), 0.92 (t, *J* = 5.1 Hz, 6H); LCMS (ESI) *m/e* 426.2 [(*M*+*H*)⁺, calcd C₂₁H₂₇F₃N₃O₃, 426.2]; LC/MS retention time (method A): *t*_R = 2.08 min.

Example 26

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)carbamate

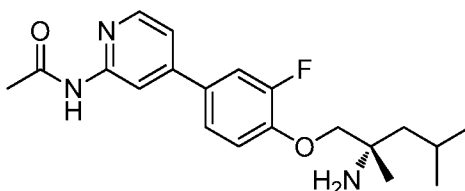


15

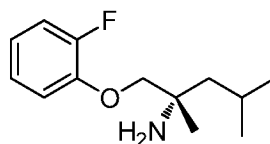
Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)carbamate (11.5 mg, 0.026 mmol, 27% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.28 (s, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.10 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.71 (s, 1H), 7.43 - 7.34 (m, 2H), 3.86 - 3.80 (m, 2H), 3.71 (s, 3H), 1.81 (dt, *J* = 12.7, 6.4 Hz, 1H), 1.39 (q, *J* = 8.2, 6.3 Hz, 2H), 1.13 (s, 3H), 0.92 (dd, *J* = 6.7, 3.8 Hz, 6H); LCMS (ESI) *m/e* 442.2 [(*M*+*H*)⁺, calcd C₂₁H₂₇F₃N₃O₄, 442.2]; LC/MS retention time (method B): *t*_R = 2.00 min.

Example 27

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

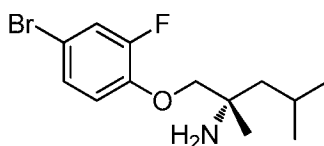


Prepared as described in Example 19.



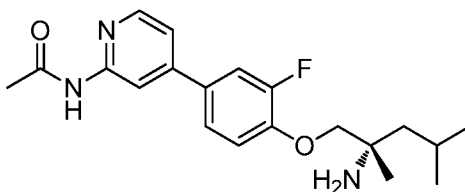
Part A: (S)-1-(2-fluorophenoxy)-2,4-dimethylpentan-2-amine.

5 LCMS (ESI) m/e 226.3 $[(M+H)^+]$, calcd $C_{13}H_{21}F_1N_1O_1$, 226.2]; LC/MS retention time (method B): t_R = 1.93 min.



Part B: (S)-1-(4-bromo-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine

10 To a 100 mL round-bottomed flask was added (*S*)-1-(2-fluorophenoxy)-2,4-dimethylpentan-2-amine (83.4 mg, 0.370 mmol) in $CHCl_3$ (2 mL) to give a colorless solution. Br_2 (0.021 mL, 0.407 mmol) was added. The mixture was stirred at 45 °C for 15 h. The reaction mixture cooled to rt and was diluted with EtOAc then treated with aqueous sodium bisulfite solution. The layers were separated. The organic
15 layer was washed with water, brine, dried (Na_2SO_4) and concentrated under reduced pressure to afford (*S*)-1-(4-bromo-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine (84 mg, 0.276 mmol, 75% yield). The crude material was carried on as is. LCMS (ESI) m/e 304.1 $[(M+H)^+]$, calcd $C_{13}H_{20}Br_1F_1N_1O_1$, 304.1]; LC/MS retention time (method A): t_R = 2.05 min.



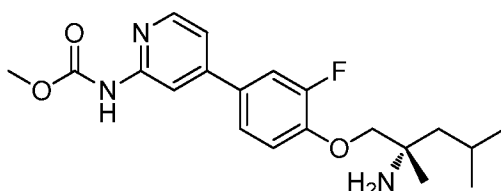
Part C: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide.

Obtained (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide (14.5 mg, 0.039 mmol, 31% yield) as an off-white solid. ^1H NMR (500 MHz, $DMSO-d_6$) δ 10.55 (s, 1H), 8.33 (d, J = 6.0 Hz,
25

2H), 7.61 (d, $J = 12.3$ Hz, 1H), 7.52 (d, $J = 8.8$ Hz, 1H), 7.39 (d, $J = 5.4$ Hz, 1H),
 7.30 (t, $J = 8.8$ Hz, 1H), 3.84 - 3.76 (m, 2H), 2.12 (s, 3H), 1.81 (p, $J = 6.4$ Hz, 1H),
 1.38 (q, $J = 7.9, 6.8$ Hz, 2H), 1.12 (s, 3H), 0.93 (t, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e
 360.2 $[(M+H)^+]$, calcd $C_{20}H_{27}F_1N_3O_2$, 360.2]; LC/MS retention time (method A): $t_R =$
 5 1.82 min.

Example 28

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-
 yl)carbamate



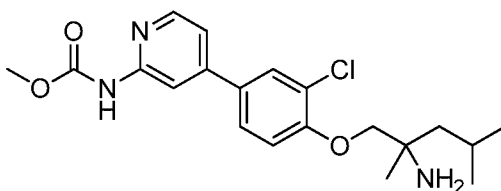
10

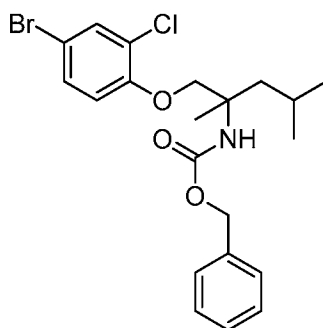
Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-
 2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate (17.1 mg, 0.044
 mmol, 30% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 10.25 (s,
 1H), 8.29 (d, $J = 5.3$ Hz, 1H), 8.09 (s, 1H), 7.62 (d, $J = 12.4$ Hz, 1H), 7.53 (d, $J =$
 15 8.6 Hz, 1H), 7.36 (d, $J = 5.4$ Hz, 1H), 7.30 (t, $J = 8.7$ Hz, 1H), 3.82 (d, $J = 2.8$ Hz,
 2H), 3.70 (s, 3H), 1.86 - 1.74 (m, 1H), 1.46 - 1.33 (m, 2H), 1.13 (s, 3H), 0.93 (t, $J =$
 6.8 Hz, 6H); LCMS (ESI) m/e 376.2 $[(M+H)^+]$, calcd $C_{20}H_{27}F_1N_3O_3$, 376.2]; LC/MS
 retention time (method A): $t_R = 1.92$ min.

20

Example 29

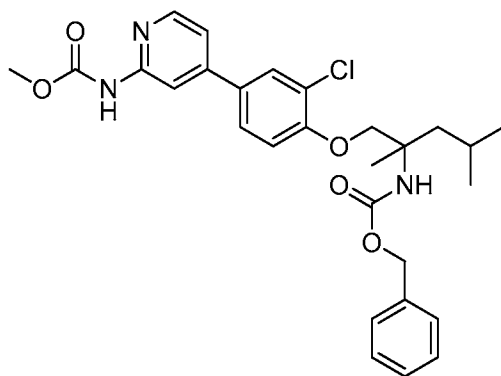
methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-
 yl)carbamate





Part A: Benzyl (1-(4-bromo-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate

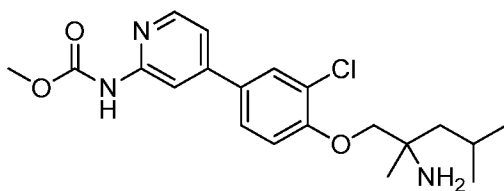
An NMP (0.3 mL) suspension of 4-bromo-2-chlorophenol (0.074 g, 0.354 mmol), potassium carbonate (0.037 g, 0.266 mmol) and benzyl 4-isobutyl-4-methyl-
 5 1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.058 g, 0.177 mmol) was heated at 50 °C overnight. The reaction was diluted with ethyl acetate and washed with NaOH (1N) (2X) and water (1X). The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude material was carried on without further purification. LCMS (ESI) *m/e* 476.1 [(M+Na)⁺, calcd
 10 C₂₁H₂₅BrClNaNO₃, 476.1]; LC/MS retention time (method B): *t_R* = 2.56 min.



Part B: Cbz methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate

A mixture of sodium carbonate (0.177 ml, 0.354 mmol), 1,1'-
 15 bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (10.12 mg, 0.012 mmol), (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.035 g, 0.177 mmol) and benzyl (1-(4-bromo-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.080 g, 0.177 mmol) in dioxane (1 mL) (degassed)
 20 was heated at 85 °C overnight. The reaction was diluted with ethyl acetate and washed with water (3X). The aqueous layer was extract with ethyl acetate. The ethyl

acetate layers were combined, washed with brine, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified via silica gel chromatography (from 0 to 30% ethyl acetate in hexanes) to give Cbz methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate (56.5 mg, 0.107 mmol, 61% yield for two steps) as a tan foam. (0.565g, 61% yield). LCMS (ESI) *m/e* 548.2 [(M+Na)⁺, calcd C₂₈H₃₂ClN₃O₅Na, 548.2]; LC/MS retention time (method B): *t*_R = 2.25 min.

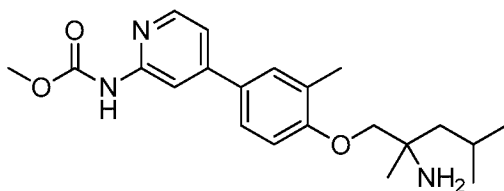


Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate

Triethylsilane(0.026 mL, 0.161 mmol) was added to a CH₂Cl₂ (0.5 mL) suspension of palladium(II) acetate(2.2 mg, 9.80 μmol) and triethylamine(1 drop) at rt. This solution was stirred at room temperature for 10 min before the addition of a CH₂Cl₂ (0.5 mL) solution of Cbz protected methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate (0.0565 g, 0.107 mmol) (the flask contain the Cbz protected methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate (0.0565 g, 0.107 mmol) was rinsed with CH₂Cl₂ (0.5 mL) and added to the reaction mixture). The above reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified via reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate (29.6mg, 0.076 mmol, 70% yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 10.27 (br. s., 1H), 8.30 (d, *J*=5.2 Hz, 1H), 8.08 (s, 1H), 7.79 (s, 1H), 7.68 (d, *J*=8.2 Hz, 1H), 7.37 (d, *J*=5.2 Hz, 1H), 7.26 (d, *J*=8.5 Hz, 1H), 3.82 (d, *J*=2.4 Hz, 2H), 3.70 (s, 3H), 1.85 - 1.77 (m, 1H), 1.42 (br. s., 2H), 1.14 (s, 3H), 0.92 (m, 6H); LCMS (ESI) *m/e* 392.2 [(M+H)⁺, calcd C₂₀H₂₇ClN₃O₃, 392.2]; LC/MS retention time (method B): *t*_R = 1.75 min.

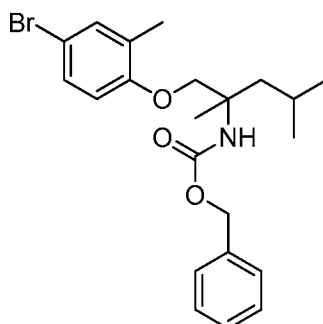
Example 30

methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate



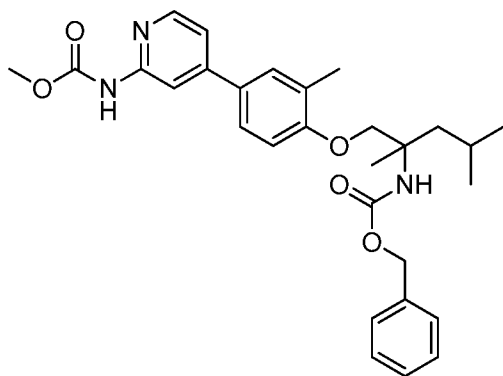
5

Prepared as described in Example 29.



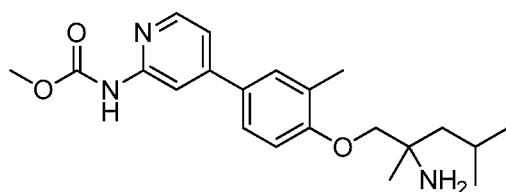
Part A: Benzyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 456.1 $[(M+Na)^+]$, calcd $C_{22}H_{28}BrNO_3Na$, 456.1]; LC/MS retention time (method B): t_R = 2.56 min.



15 Part B: Cbz methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate.

LCMS (ESI) m/e 506.1 $[(M+H)^+]$, calcd $C_{29}H_{36}N_3O_5$, 506.3]; LC/MS retention time (method B): t_R = 2.21 min.

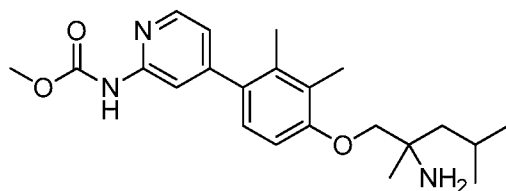


Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate.

Obtained methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate (3.7 mg, 9.96 μmol , 35% yield) as an off white solid. ^1H NMR (600MHz, DMSO- d_6) δ 10.11 (br. s., 1H), 8.26 (d, $J=5.1$ Hz, 1H), 8.08 (s, 1H), 7.53 (br. s., 2H), 7.34 - 7.27 (m, 1H), 7.03 (d, $J=9.2$ Hz, 1H), 3.77 - 3.68 (m, 5H), 2.28 (s, 3H), 1.86 - 1.76 (m, 1H), 1.42 (t, $J=5.0$ Hz, 2H), 1.14 (s, 3H), 0.93 (m, 6H); LCMS (ESI) m/e 372.3 $[(M+H)^+]$, calcd $\text{C}_{21}\text{H}_{30}\text{N}_3\text{O}_3$, 372.2; LC/MS retention time (method B): t_R = 1.71 min.

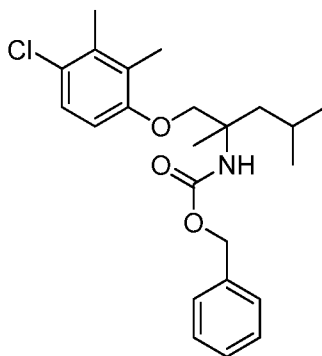
Example 31

methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate



15

Prepared as described in Example 29.

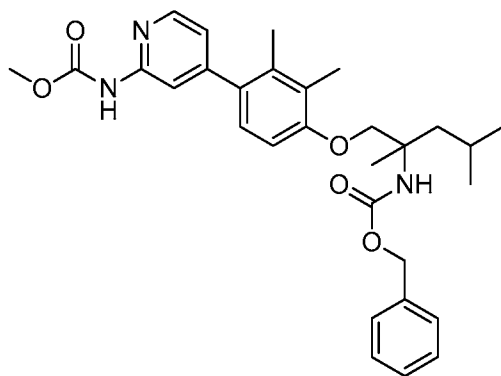


20

Part A: Benzyl (1-((5-chloro-3,4-dimethylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

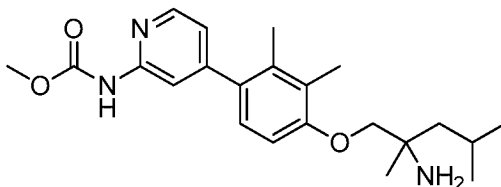
LCMS (ESI) m/e 426.3 $[(M+Na)^+]$, calcd $C_{22}H_{29}ClN_2O_3Na$, 427.2; LC/MS retention time (method B): t_R = 2.57 min.

5



Part B: Cbz methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate.

A mixture of 2nd generation Xphos Precatalyst (4 mg, 5.08 μ mol), potassium
 10 phosphate tribasic (0.5 mL, 0.250 mmol), (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.044 g, 0.225 mmol) and benzyl (1-(4-chloro-2,3-dimethylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.0385g, 0.095 mmol) in THF (0.8 mL) was degassed via vacuum/ N_2 fill cycle three times. The reaction mixture was heated at 80 °C overnight. The reaction was diluted with ethyl acetate
 15 and washed with water (2X) followed by brine. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The product was purified via silica gel chromatography (0-30% ethyl acetate in hexanes) to afford Cbz methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate (25 mg, 0.025 mmol, 27% yield) as a white
 20 solid. LCMS (ESI) m/e 520.5 $[(M+H)^+]$, calcd $C_{30}H_{37}N_3O_5$, 520.3; LC/MS retention time (method A): t_R = 2.38 min.

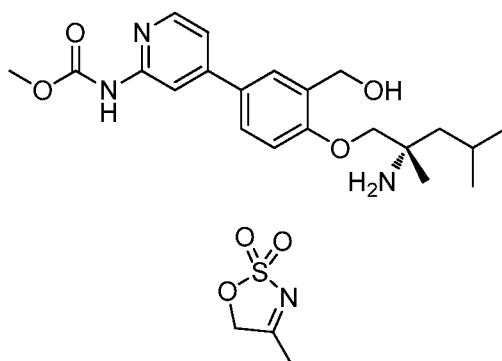


Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate

A mixture of Pd/C (6 mg, 5.64 μ mol) and Cbz protected methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate (0.025 g, 0.048 mmol) in ethanol (4 mL) was hydrogenated via a H₂ balloon at room temperature overnight. The reaction mixture was filtered through a celite pad and washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate (2.8 mg, 7.26 μ mol, 15% yield) as an off-white solid. ¹H NMR (600MHz, DMSO-d₆) δ 8.26 (d, *J*=4.8 Hz, 1H), 7.74 (s, 1H), 7.02 (d, *J*=8.4 Hz, 1H), 6.96 (d, *J*=5.1 Hz, 1H), 6.86 (d, *J*=8.8 Hz, 1H), 3.67 (s, 4H), 3.48 (d, *J*=10.6 Hz, 1H), 2.19 (s, 3H), 1.84 (s, 3H), 1.83 - 1.74 (m, 1H), 1.42 (t, *J*=6.1 Hz, 2H), 1.14 (s, 3H), 0.92 (t, *J*=5.9 Hz, 6H). LCMS (ESI) *m/e* 369.2 [(M-NH₂)⁺, calcd C₂₂H₂₉N₂O₃, 369.2]; LC/MS retention time (method B): *t*_R = 1.68 min.

Example 32

(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl)carbamate



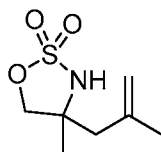
Part A. 4-methyl-5H-1,2,3-oxathiazole 2,2-dioxide

Step 1: Sulfamoyl chloride formation: In a 1000ml 4 neck round-bottomed flask equipped with a mechanical stirring and an addition funnel, was charged DCM (400 mL) and chlorosulfonyl isocyanate (124 mL, 1430 mmol). Under N₂, this solution was cooled to 0 °C. Then formic acid (53.9 mL, 1430 mmol) was added to DCM (100 mL) and this solution was transferred to the addition funnel and the solution was added slowly to the vigorously stirring reaction mixture. Gradually a

thick slurry formed. A slow exotherm was observed so additional dry ice was added to acetone bath. Once temperature was stabilized, addition of the formic acid was continued. Addition was done in ~ 25 min. The mixture was allowed to gradually warm to room temperature and was stirred overnight.

5 Step 2: In a separate 5L 4 neck reaction flask was charged hydroxyacetone (72.5 mL, 953 mmol), pyridine (116 mL, 1430 mmol), and DCM (2000 mL). This solution was cooled to -5°C under N₂. The sulfamoyl chloride solution was added slowly via Teflon tube over 10 min. After the addition, the reaction was stirred for 15 min then the ice bath was removed and the reaction mixture allowed to warm to
10 room temperature. As the reaction progressed, a gummy material formed. The material was purified via silica gel chromatography (300 g silica gel eluting with DCM). Obtained 4-methyl-5H-1,2,3-oxathiazole 2,2-dioxide (72.4 g, 536 mmol, 56 % yield) as a colorless solid. ¹H NMR (400MHz, CHLOROFORM-d) δ 5.09 (s, 2H), 2.44 (s, 3H); LCMS (ESI) *m/e* 136.0 [(M+H)⁺, calcd for C₃H₆NO₃S 136.0].

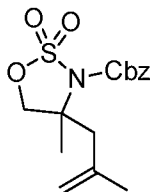
15



Part B. 2-(tert-butoxycarbonylamino)-2,4-dimethylpentanoic acid 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine 2,2-dioxide

A suspension of 4-methyl-5H-1,2,3-oxathiazole 2,2-dioxide (0.541 g, 4mmol)
20 in methyl *tert*-butyl ether (30 mL) was cooled below 0 °C with an ice/IPA bath. To the cooled solution was added a solution of (2-methylallyl)magnesium chloride, 0.5 M in THF (9.60 mL, 4.80 mmol). The reaction mixture was allowed to warm to rt overnight. It was then quenched with a saturated solution of NH₄Cl (50 mL) and EtOAc (20 mL) was added. The organic phase was separated, washed with brine (50
25 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 2-(*tert*-butoxycarbonylamino)-2,4-dimethylpentanoic acid 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine 2,2-dioxide (0.567 g, 2.96 mmol, 74 % yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 5.06 (quin, *J*=1.5 Hz, 1H), 4.87 (dd, *J*=1.7, 0.8 Hz, 1H), 4.50 (br. s., 1H), 4.40 (d, *J*=8.6 Hz, 1H), 4.29 (d, *J*=8.7 Hz, 1H), 2.56 (d,

$J=13.8$ Hz, 1H), 2.40 - 2.30 (m, 1H), 1.86 (br. s, 3H), 1.49 (s, 3H); LCMS (ESI) m/e 192.1 [(M+H)⁺, calcd for C₇H₁₄NO₃S 192.1].



5 Part C. benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide

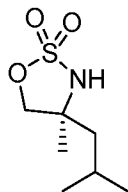
To a N₂ flushed, 100 mL round-bottomed flask was added a solution of 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine 2,2-dioxide (0.55 g, 2.88 mmol) in THF (10 mL). A solution of potassium *tert*-butoxide (4.31 mL, 4.31 mmol) in THF
10 was added. The temperature rose to 27 °C and the solution became a suspension. The mixture was stirred at room temperature for 1 h. Benzyl carbonochloridate (1.026 mL, 7.19 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with water (50 mL) and extracted with EtOAc (2x70 mL). The organic extracts were washed with brine
15 (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate/hexanes) to give benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.66 g, 2.028 mmol, 71 % yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.58 - 7.32 (m, 5H), 5.43 - 5.25 (m, 2H), 5.01 (t, $J=1.5$ Hz, 1H), 4.81 (d, $J=0.9$ Hz, 1H),
20 4.63 (d, $J=9.5$ Hz, 1H), 4.21 (d, $J=9.5$ Hz, 1H), 2.87 (d, $J=14.1$ Hz, 1H), 2.56 (d, $J=14.1$ Hz, 1H), 1.78 (br. s, 3H), 1.64 (s, 3H); LCMS (ESI) m/e 326.1 [(M+H)⁺, calcd for C₁₅H₂₀NO₅S 326.1].

The racemic compounds was separated by chiral super critical fluid chromatography (Column: OJ-H (3x25cm, 5μm); Mobile Phase: CO₂/ MeOH
25 (90/10)) to give the two enantiomers.

Analytical super critical fluid chromatography conditions: Column: OJ-H (0.46x25cm, 5μm); BPR pressure: 100 bars; Temperature: 35 °C; Flow rate: 3.0 mL/min; Mobile Phase: CO₂/ MeOH (90/10); Detector Wavelength: UV 200-400nm

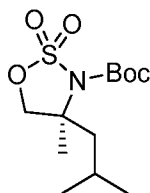
Enantiomer 1: (*S*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 2.53 min.
30

Enantiomer 2: (*R*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 2.97 min.



5 *Part D. (S)-4-isobutyl-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide*

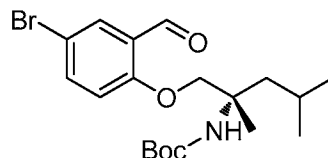
To a stirred solution of (*S*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (800 mg, 2.459 mmol) in MeOH (20 mL) was added Pd/C (262 mg, 0.246 mmol) under a nitrogen atmosphere and the reaction mixture was stirred under 1 atm hydrogen pressure for 16 h. The reaction mixture
 10 was passed through celite pad and the celite pad was washed with EtOAc (15 mL). The organic layer was evaporated under reduced pressure to afford (*S*)-4-isobutyl-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide (462 mg, 2.39 mmol, 97% yield, 95% purity) as colorless oil. The material was carried forward without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.69 (br, 1H) 4.33 (d, *J*=8.03
 15 Hz, 1 H) 4.17 - 4.26 (m, 1 H) 1.68 - 1.81 (m, 1 H) 1.53 - 1.63 (m, 1 H) 1.43 - 1.51 (m, 1 H) 1.34 (s, 3 H) 0.81 - 1.00 (m, 6 H).



20 *Part E. (S)-tert-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide*

To a stirred solution of (*S*)-4-isobutyl-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide (7 g, 15.21 mmol) in DCM (70 mL) cooled to 0 °C was added DMAP (1.858 g, 15.21 mmol) and (BOC)₂O (5.30 mL, 22.82 mmol). The reaction mixture was stirred at rt for 12 h. The reaction mixture was transferred to a separating funnel
 25 containing water (20 mL) and was extracted with DCM (2 x 60 mL). The combined organic layers were washed with brine (50 mL), dried over (Na₂SO₄), and concentrated under reduced pressure. The residue was purified via silica gel

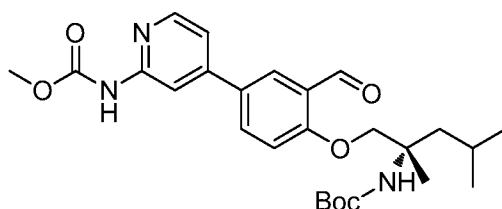
chromatography (30 % ethyl acetate in pet ether) to afford (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (4.4 g, 14.70 mmol, 97 % yield) as a colorless oil. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 4.45 (d, *J*=9.0 Hz, 1H), 4.20 (d, *J*=9.0 Hz, 1H), 2.07 - 1.98 (m, *J*=8.0 Hz, 1H), 1.83 - 1.69 (m, 2H),
 5 1.59 (s, 3H), 1.56 (s, 9H), 0.99 (dd, *J*=8.0, 6.5 Hz, 6H).



Part F: (S)-tert-butyl (1-(4-bromo-2-formylphenoxy)-2,4-dimethylpentan-2-yl)carbamate.

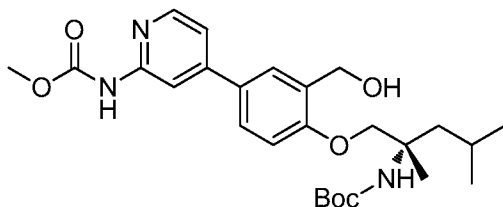
10 To a 20 mL vial was added 5-bromo-2-hydroxybenzaldehyde (81 mg, 0.403 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (107.4 mg, 0.366 mmol), and K₂CO₃ (152 mg, 1.098 mmol) in DMF (1.2 mL) to give a white suspension. The vial was sealed and the mixture was heated at 80 °C for 17 h. The reaction mixture was cooled to rt and partitioned between water
 15 and EtOAc. The layers were separated. The organic layer was washed with water, brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (up to 40% EtOAc/hexanes) to afford (*S*)-*tert*-butyl (1-(4-bromo-2-formylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (115 mg, 0.278 mmol, 76%) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ
 20 10.43 (s, 1H), 7.89 (d, *J* = 2.6 Hz, 1H), 7.59 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.58 (s, 1H), 4.29 (d, *J* = 8.8 Hz, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 1.94 - 1.74 (m, 2H), 1.48 (dd, *J* = 13.9, 4.8 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 9H), 0.98 (dd, *J* = 6.6, 4.8 Hz, 6H); (ESI) *m/e* 314.0, 316.0 Br pattern [(M-Boc+H)⁺, calcd C₁₄H₂₁BrNO₂, 414.1]; LC/MS retention time (method B): *t*_R = 2.39 min.

25



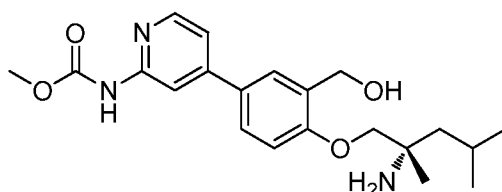
Part G: (S)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-carbonylphenyl)pyridin-2-yl)carbamate.

To a 2 mL vial was added (*S*)-*tert*-butyl (1-(4-bromo-2-formylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (27.9 mg, 0.067 mmol), (2-
 5 ((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (19.79 mg, 0.101 mmol), and Na₂CO₃ (0.101 mL, 0.202 mmol) in dioxane (0.5 mL) under nitrogen to give a colorless suspension. 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene (2.77 mg, 3.37 μmol) was added under nitrogen. The vial was sealed and heated at 100 °C (bath temp: 105°C) for 3 h. LCMS showed conversion to the
 10 desired product (M + H = 486), but with some starting material left. A bit more reagents was added and heating continued for another 3h. LCMS showed no more starting material. The mixture was diluted with EtOAc and passed through a plug of Na₂SO₄. The organic solution was concentrated. Obtained (*S*)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-carbonylphenyl)pyridin-2-yl)carbamate as a tan
 15 residue which was carried on without further purification. LCMS (ESI) *m/e* 486.4 [(M+H)⁺, calcd C₂₆H₃₆N₃O₆, 486.3]; LC/MS retention time (method C): *t_R* = 4.23 min.



20 *Part H: (S)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl)carbamate*

To a 2 mL vial was added crude aldehyde (10.68 mg, 0.022 mmol) in MeOH (0.5 mL) to give a tan solution. NaBH₄ (5 mg, 0.132 mmol) was added. The mixture was stirred at rt for 1 h. The mixture was partitioned between water and EtOAc. The
 25 layers were separated. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The tan residue was directly carried onto next reaction. LCMS (ESI) *m/e* 488.2 [(M+H)⁺, calcd C₂₆H₃₈N₃O₆, 488.3]; LC/MS retention time (method B): *t_R* = 2.00 min.

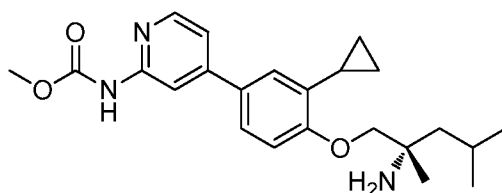


Part I: (S)-methyl 4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl carbamate

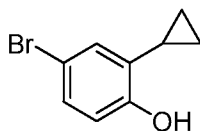
To a 25 mL flask was added (S)-methyl 4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl carbamate (10.73 mg, 0.022 mmol) in CH₂Cl₂ (1 mL) to give a tan solution. TFA (0.5 mL, 6.49 mmol) was added under nitrogen. The mixture was stirred at rt for 1 h. The mixture was concentrated. The residue was dissolved in MeOH, filtered, and purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford (S)-methyl 4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl carbamate (7.6 mg, 0.019 mmol, 86% yield for three steps) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.28 (d, *J* = 5.2 Hz, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.32 (d, *J* = 5.2 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 4.63 (s, 2H), 3.77 (s, 2H), 3.70 (s, 3H), 1.79 (td, *J* = 11.7, 10.6, 5.5 Hz, 1H), 1.42 (qd, *J* = 14.0, 5.6 Hz, 2H), 1.14 (s, 3H), 0.93 (t, *J* = 7.2 Hz, 6H); LCMS (ESI) *m/e* 388.1 [(M+H)⁺, calcd C₂₁H₃₀N₃O₄, 388.2]; LC/MS retention time (method B): *t_R* = 1.55 min.

Example 33

(S)-methyl 4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyclopropylphenyl)pyridin-2-yl carbamate

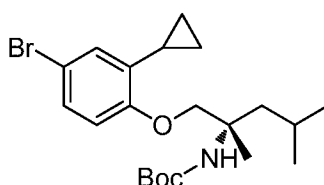


Prepared as described in Example 32.



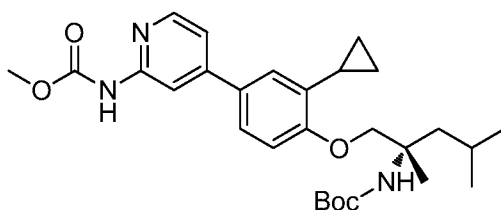
Part A: (S)-tert-butyl (1-(4-bromo-2-cyclopropylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a 100 mL round-bottomed flask was added 2-cyclopropylphenol (584 mg, 4.35 mmol) in CH₂Cl₂ (22 mL) to give a colorless solution. Br₂ (0.224 mL, 4.35 mmol) was added dropwise at 0°C. The mixture was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure to afford (S)-tert-butyl (1-(4-bromo-2-cyclopropylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (992 mg, 4.35 mmol, 100% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-d) δ 7.24 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.20 (dd, *J* = 2.5, 0.9 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 1H), 5.43 (s, 1H), 1.82 (tt, *J* = 8.3, 5.3 Hz, 1H), 1.04 - 0.97 (m, 2H), 0.70 - 0.64 (m, 2H); LC/MS retention time (method B): *t*_R = 2.09 min.



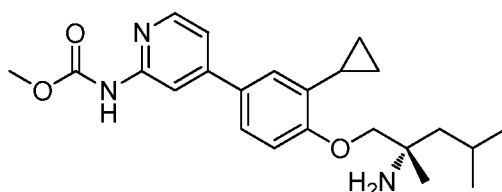
Part B: (S)-tert-butyl (1-(4-bromo-2-cyclopropylphenoxy)-2,4-dimethylpentan-2-yl)carbamate.

¹H NMR (400 MHz, Chloroform-d) δ 7.21 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.67 (s, 1H), 4.10 (d, *J* = 9.0 Hz, 1H), 3.94 (d, *J* = 8.8 Hz, 1H), 2.16 - 2.08 (m, 1H), 1.84 (ddt, *J* = 13.0, 10.9, 6.5 Hz, 2H), 1.69 - 1.59 (m, 1H), 1.43 (s, 3H), 1.42 (s, 9H), 0.99 (dd, *J* = 6.5, 3.1 Hz, 6H), 0.97 - 0.92 (m, 2H), 0.68 - 0.61 (m, 2H); LCMS (ESI) *m/e* 447.9 [(M+Na)⁺, calcd C₂₁H₃₂BrN₁Na₁O₃, 448.2]; LC/MS retention time (method B): *t*_R = 2.59 min.



Part C: (S)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-cyclopropylphenyl)pyridin-2-yl)carbamate.

LCMS (ESI) *m/e* 498.1 [(M+H)⁺, calcd C₂₈H₄₀N₃O₅, 498.3]; LC/MS retention time (method B): *t*_R = 2.24 min.



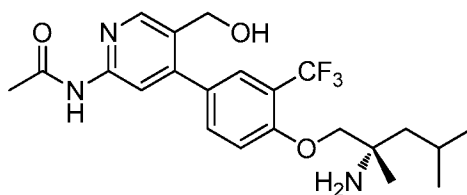
Part D: *(S)*-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyclopropylphenyl)pyridin-2-yl)carbamate.

¹H NMR (500 MHz, DMSO-d₆) δ 8.25 (d, *J* = 5.3 Hz, 1H), 8.05 (s, 1H), 7.50 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 3.81 - 3.73 (m, 2H), 3.70 (s, 3H), 2.20 (ddd, *J* = 13.9, 8.8, 5.4 Hz, 1H), 1.82 (dt, *J* = 12.8, 6.3 Hz, 1H), 1.49 - 1.38 (m, 2H), 1.16 (s, 3H), 0.94 (q, *J* = 6.2 Hz, 8H), 0.72 (q, *J* = 5.1 Hz, 2H); LCMS (ESI) *m/e* 398.1 [(M+H)⁺, calcd C₂₃H₃₂N₃O₃, 398.2]; LC/MS retention time (method B): *t*_R = 1.73 min.

10

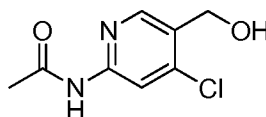
Example 34

(S)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-5-(hydroxymethyl)pyridin-2-yl)acetamide



15

Prepared as described in Example 19.

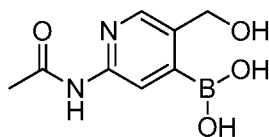


Part A: *N*-(4-chloro-5-(hydroxymethyl)pyridin-2-yl)acetamide

To a 25 mL vial was added (4,6-dichloropyridin-3-yl)methanol (125.8 mg, 0.707 mmol), and acetamide (62.6 mg, 1.060 mmol) in 1,4-dioxane (4 mL) to give a colorless solution. While degassing with N₂, PdOAc₂ (7.93 mg, 0.035 mmol), XANTPHOS (30.7 mg, 0.053 mmol), Cs₂CO₃ (368 mg, 1.131 mmol) were added. The vial was sealed under nitrogen and heated at 110 °C (bath: 112°C) for 22 h (1:30pm). The reaction mixture was cooled to rt and partitioned between water and EtOAc. There were some insoluble solids which were removed by filtration. The

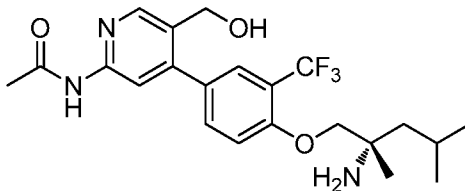
25

layers were separated. The aqueous layer was extracted 4 times with EtOAc (there were still product left in aq.). The combined organic layers were washed with brine, dried and concentrated. The residue was purified by silica gel chromatography (up to 10% MeOH/CH₂Cl₂) to afford *N*-(4-chloro-5-(hydroxymethyl)pyridin-2-yl)acetamide (90 mg, 0.449 mmol, 64% yield) as a white solid: ¹H NMR (400 MHz, Methanol-d₄) δ 8.34 (s, 1H), 8.19 (s, 1H), 4.69 (s, 2H), 2.19 (s, 3H); LCMS (ESI) *m/e* 201.1 [(M+H)⁺, calcd C₈H₁₀ClN₂O₂, 201.1]; LC/MS retention time (method B): *t_R* = 1.73 min.



Part B: (2-acetamido-5-(hydroxymethyl)pyridin-4-yl)boronic acid

To a 20 mL vial was added *N*-(4-chloro-5-(hydroxymethyl)pyridin-2-yl)acetamide (48 mg, 0.239 mmol), hypodiboric acid (32.2 mg, 0.359 mmol), 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (2.281 mg, 4.79 μmol), Xphos precatalyst (1.882 mg, 2.393 μmol) and potassium acetate (70.4 mg, 0.718 mmol) in ethanol (2.2 mL) to give a tan suspension (degassed with N₂ before adding reagents). The bottle was capped and heated at 80 °C for 1.5 h. The mixture was cooled to rt and concentrated under reduced pressure. The crude material was carried on without purification.



Part C: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-5-(hydroxymethyl)pyridin-2-yl)acetamide

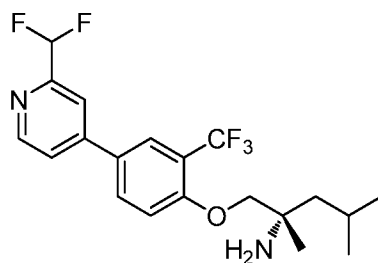
To a 20 mL vial was added (2-acetamido-5-(hydroxymethyl)pyridin-4-yl)boronic acid (50.2 mg, 0.239 mmol) was added potassium phosphate tribasic (2 mL, 1.000 mmol). After degassing with N₂ for 5 min, Xphos precatalyst (3.76 mg, 4.78 μmol) and (*S*)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (30 mg, 0.076 mmol) (prepared as described in Example 19. Part A) in

tetrahydrofuran (2 mL) were added. The vial was sealed and heated at 80 °C for 18 h. The reaction mixture was cooled to rt and the volatiles were removed under reduced pressure. The residue was partitioned between water and EtOAc. The organic layer was dried, filtered and concentrated. The residue was dissolved in MeOH and purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-5-(hydroxymethyl)pyridin-2-yl)acetamide (27.7 mg, 0.060 mmol, 79% yield) as an off-white solid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 8.38 (s, 1H), 8.02 (s, 1H), 7.80 (s, 1H), 7.78 - 7.71 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 4.36 (s, 2H), 3.86 (q, *J* = 8.8 Hz, 2H), 2.10 (s, 3H), 1.81 (dt, *J* = 12.6, 6.1 Hz, 1H), 1.45 - 1.37 (m, 2H), 1.13 (s, 3H), 0.92 (dd, *J* = 6.6, 3.4 Hz, 6H); LCMS (ESI) *m/e* 440.2 [(*M*+*H*)⁺, calcd C₂₂H₂₉F₃N₃O₃, 440.2]; LC/MS retention time (method B): *t*_R = 1.67 min.

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Example 35

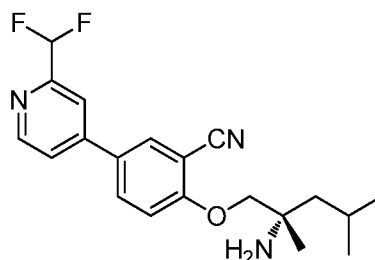
(*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 19. Obtained (*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (25.5 mg, 0.062 mmol, 54% yield) as an off-white solid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.74 (d, *J* = 5.1 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.11 (s, 1H), 8.06 (s, 1H), 7.96 (d, *J* = 5.1 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.01 (t, *J* = 54.9 Hz, 1H), 4.05 (q, *J* = 9.6 Hz, 2H), 1.81 (dt, *J* = 12.9, 6.6 Hz, 1H), 1.61 - 1.47 (m, 2H), 1.25 (s, 3H), 0.92 (t, *J* = 6.9 Hz, 6H); LCMS (ESI) *m/e* 403.4 [(*M*+*H*)⁺, calcd C₂₀H₂₄F₅N₂O₁, 403.2]; LC/MS retention time (method A): *t*_R = 2.13 min.

Example 36

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyridin-4-yl)benzonitrile

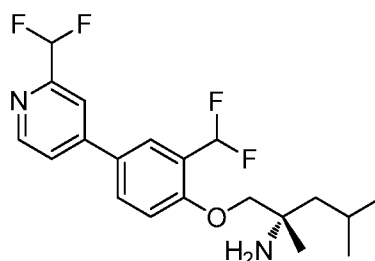


5 Prepared as described in Example 19. Obtained (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyridin-4-yl)benzonitrile (32 mg, 0.086 mmol, 60% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 2.5 Hz, 1H), 7.95 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.80 (s, 1H), 7.69 (d, *J* = 5.2 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 1H), 6.73 (t, *J* = 54.8 Hz, 1H), 3.80 -
10 3.68 (m, 2H), 1.56 (dp, *J* = 12.5, 6.4 Hz, 1H), 1.23 (qd, *J* = 14.0, 5.5 Hz, 2H), 0.95 (s, 3H), 0.68 (dd, *J* = 6.7, 4.7 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -115.30 (d, *J* = 54.0 Hz); LCMS (ESI) *m/e* 360.2 [(*M*+*H*)⁺, calcd C₂₀H₂₄F₂N₃O₁, 360.2]; LC/MS retention time (method B): *t*_R = 1.69 min.

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Example 37

(*S*)-1-(2-(difluoromethyl)-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



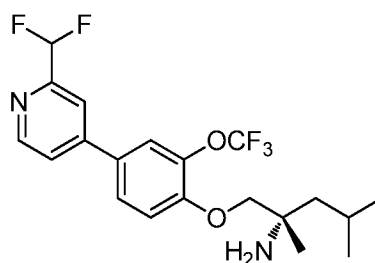
20 Prepared as described in Example 19. Obtained (*S*)-1-(2-(difluoromethyl)-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (31.9 mg, 0.080 mmol, 61% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.1 Hz, 1H), 7.81 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 2H), 7.67 (d, *J* = 5.1 Hz, 1H), 7.22 - 6.94 (m, 2H), 6.76 (t, *J* = 54.9 Hz, 1H), 3.68 (d, *J* = 2.2 Hz, 2H), 1.54 (dp, *J* = 12.7, 6.3 Hz, 1H), 1.30 - 1.13 (m, 2H), 0.95 (s, 3H), 0.67

(dd, $J = 15.9, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -73.65, -115.33; LCMS (ESI) m/e 407.2 $[(M+\text{Na})^+]$, calcd $\text{C}_{20}\text{H}_{24}\text{F}_4\text{N}_2\text{Na}_1\text{O}_1$, 407.2; LC/MS retention time (method B): $t_R = 1.89$ min.

5

Example 38

(*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine

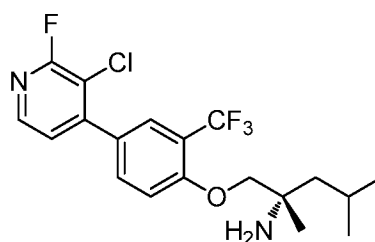


Prepared as described in Example 19. Obtained (*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine (21.1 mg, 0.050 mmol, 39% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.55 (d, $J = 5.2$ Hz, 1H), 7.85 (s, 1H), 7.78 (dd, $J = 13.4, 5.4$ Hz, 3H), 7.22 (d, $J = 8.6$ Hz, 1H), 6.83 (t, $J = 54.9$ Hz, 1H), 3.71 (d, $J = 3.6$ Hz, 2H), 1.64 (dt, $J = 12.7, 6.3$ Hz, 1H), 1.26 (dq, $J = 14.8, 8.3, 6.9$ Hz, 2H), 0.98 (s, 3H), 0.75 (t, $J = 5.9$ Hz, 6H); LCMS (ESI) m/e 419.3 $[(M+\text{H})^+]$, calcd $\text{C}_{20}\text{H}_{24}\text{F}_5\text{N}_2\text{O}_2$, 419.2; LC/MS retention time (method B): $t_R = 2.03$ min.

20

Example 39

(*S*)-1-(4-(3-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 19. Obtained (*S*)-1-(4-(3-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (14 mg, 0.035 mmol, 42% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.25 (d, $J = 5.1$ Hz, 1H), 7.88 - 7.79 (m, 2H), 7.53 (d, $J = 5.1$ Hz, 1H), 7.40 (d, $J =$

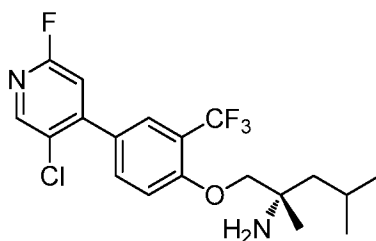
25

8.5 Hz, 1H), 3.87 (q, $J = 8.9$ Hz, 2H), 1.80 (hept, $J = 6.5$ Hz, 1H), 1.39 (d, $J = 5.6$ Hz, 2H), 1.12 (s, 3H), 0.92 (dd, $J = 6.7, 2.4$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.18, -71.35; LCMS (ESI) m/e 405.1 $[(M+H)^+]$, calcd $\text{C}_{19}\text{H}_{22}\text{Cl}_1\text{F}_4\text{N}_2\text{O}_1$, 405.1]; LC/MS retention time (method B): $t_R = 2.04$ min.

5

Example 40

(*S*)-1-(4-(5-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

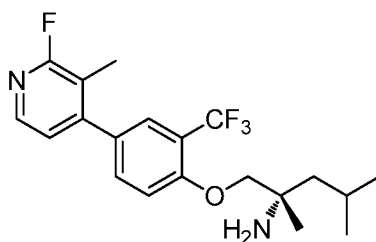


10 Prepared as described in Example 19. Obtained (*S*)-1-(4-(5-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (15.2 mg, 0.037 mmol, 43% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.45 (s, 1H), 7.88 - 7.80 (m, 2H), 7.46 (d, $J = 1.9$ Hz, 1H), 7.39 (d, $J = 8.5$ Hz, 1H), 3.93 - 3.82 (m, 2H), 1.80 (dp, $J = 12.8, 6.5$ Hz, 1H), 1.40 (d, $J = 5.5$ Hz, 2H), 1.13 (s, 3H), 0.92 (dd, $J = 6.6, 2.5$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.16, -71.37; LCMS (ESI) m/e 405.1 $[(M+H)^+]$, calcd $\text{C}_{19}\text{H}_{22}\text{Cl}_1\text{F}_4\text{N}_2\text{O}_1$, 405.1]; LC/MS retention time (method B): $t_R = 2.04$ min.

15

Example 41

20 (*S*)-1-(4-(2-fluoro-3-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



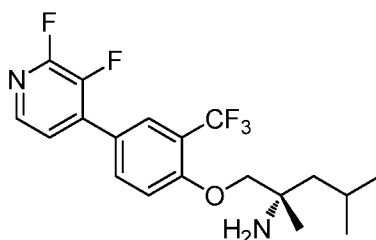
Prepared as described in Example 19. Obtained (*S*)-1-(4-(2-fluoro-3-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (14.1 mg, 0.036 mmol, 42% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ

25

8.10 (d, $J = 5.1$ Hz, 1H), 7.72 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.67 (d, $J = 2.2$ Hz, 1H), 7.36 (d, $J = 8.6$ Hz, 1H), 7.29 (d, $J = 5.1$ Hz, 1H), 3.87 (q, $J = 8.8$ Hz, 2H), 2.17 (s, 3H), 1.81 (dp, $J = 12.7, 6.4$ Hz, 1H), 1.46 - 1.35 (m, 2H), 1.13 (s, 3H), 0.92 (dd, $J = 6.7, 2.8$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.03, -71.80; LCMS (ESI) m/e 385.2 $[(M+H)^+]$, calcd $\text{C}_{20}\text{H}_{25}\text{F}_4\text{N}_2\text{O}_1$, 385.2]; LC/MS retention time (method B): $t_R = 1.99$ min.

Example 42

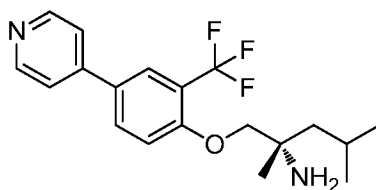
(*S*)-1-(4-(2,3-difluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 19. Obtained (*S*)-1-(4-(2,3-difluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (7 mg, 0.018 mmol, 21% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.10 (d, $J = 5.1$ Hz, 1H), 7.99 (d, $J = 8.7$ Hz, 1H), 7.95 (d, $J = 2.3$ Hz, 1H), 7.66 (t, $J = 5.1$ Hz, 1H), 7.43 (d, $J = 8.8$ Hz, 1H), 3.90 (q, $J = 8.8$ Hz, 2H), 1.79 (dq, $J = 12.8, 6.4$ Hz, 1H), 1.40 (d, $J = 5.5$ Hz, 2H), 1.13 (s, 3H), 0.92 (dd, $J = 6.6, 2.2$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -61.23, -89.72, -89.79; LCMS (ESI) m/e 389.2 $[(M+H)^+]$, calcd $\text{C}_{19}\text{H}_{22}\text{F}_5\text{N}_2\text{O}_1$, 389.2]; LC/MS retention time (method B): $t_R = 2.01$ min.

Example 43

(*S*)-2,4-dimethyl-1-(4-(pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

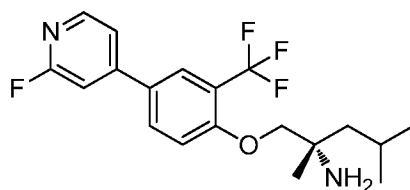


Prepared as described in Example 19. A mixture of sodium carbonate (0.068 mL, 0.136 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (3.89 mg, 4.76 μmol), pyridin-4-ylboronic acid (8.36 mg,

0.068 mmol) and (*S*)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (0.0241 g, 0.068 mmol) in dioxane (0.5 mL) (degassed with N₂) was heated at 80 °C overnight. The reaction mixture was cooled to rt and diluted with ethyl acetate then washed with water (3X). The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate). Obtained (*S*)-2,4-dimethyl-1-(4-(pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (89 mg, 0.088 mmol, 46% yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 8.62 (d, *J*=5.9 Hz, 2H), 8.09 (d, *J*=9.2 Hz, 1H), 8.01 (s, 1H), 7.75 (d, *J*=5.5 Hz, 2H), 7.37 (d, *J*=8.8 Hz, 1H), 3.87 (d, *J*=7.0 Hz, 2H), 1.84 - 1.74 (m, 1H), 1.39 (d, *J*=5.5 Hz, 2H), 1.12 (s, 3H), 0.91 (d, *J*=6.6 Hz, 6H) LCMS (ESI) *m/e* 353.2 [(*M*+H)⁺, calcd C₁₉H₂₄F₃N₂O, 353.2]; LC/MS retention time (method B): *t_R* = 1.48 min.

Example 44

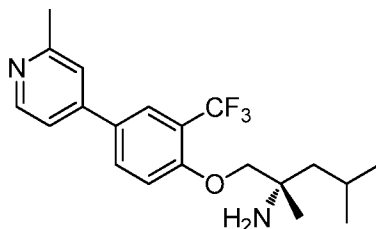
(*S*)-1-(4-(2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 43. Obtained (*S*)-1-(4-(2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (9.3 mg, 0.025 mmol, 36% yield) as an off-white solid. ¹H NMR (400MHz, METHANOL-d₄) δ 8.27 (d, *J*=5.4 Hz, 1H), 8.10 - 8.04 (m, 2H), 7.63 (d, *J*=5.4 Hz, 1H), 7.45 - 7.39 (m, 2H), 4.19 (d, *J*=3.2 Hz, 2H), 1.94 (s, 3H), 1.77 (d, *J*=5.6 Hz, 2H), 1.71 - 1.63 (m, 1H), 1.45 (s, 2H), 1.04 (d, *J*=6.6 Hz, 3H), 1.02 (d, *J*=6.6 Hz, 3H); LCMS (ESI) *m/e* 371.2 [(*M*+H)⁺, calcd C₁₉H₂₃F₄N₂O, 371.2]; LC/MS retention time (method B): *t_R* = 1.95 min.

Example 45

(*S*)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

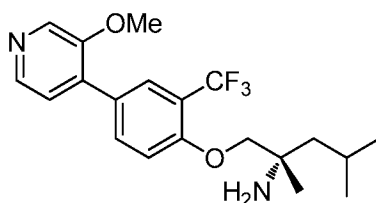


5 Prepared as described in Example 19. Obtained (*S*)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (16 mg, 0.044 mmol, 50% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.68 (d, *J* = 5.8 Hz, 1H), 8.26 (dd, *J* = 8.8, 2.6 Hz, 1H), 8.19 - 8.18 (m, 1H), 8.04 (s, 1H), 7.94 (d, *J* = 5.9 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 4.26 (q, *J* = 10.1 Hz, 2H), 2.66 (s, 3H),
 10 1.83 (dq, *J* = 13.0, 6.5 Hz, 1H), 1.74 (dd, *J* = 14.3, 5.5 Hz, 1H), 1.62 (dd, *J* = 14.6, 5.8 Hz, 1H), 1.40 (s, 3H), 0.93 (dd, *J* = 8.6, 6.4 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -60.51, -73.76 (TFA); LCMS (ESI) *m/e* 367.2 [(*M*+H)⁺, calcd C₂₀H₂₆F₃N₂O₁, 367.2]; LC/MS retention time (method B): *t*_R = 1.51 min.

15

Example 46

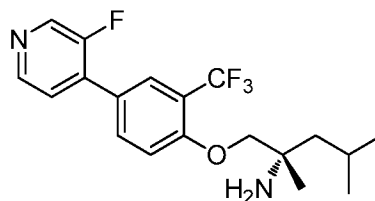
(*S*)-1-(4-(3-methoxypyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 19. Obtained (*S*)-1-(4-(3-methoxypyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (8.5 mg, 0.021 mmol, 24% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.47 (s, 1H), 8.28 (d, *J* = 4.8 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 3.91 (s, 3H), 3.86 (q, *J* = 8.9 Hz, 2H), 1.80 (hept, *J* = 6.4 Hz, 1H), 1.40 (d, *J* = 5.5 Hz, 2H), 1.13 (s, 3H), 0.92 (dd, *J* = 6.8, 2.5 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.00; LCMS (ESI) *m/e* 383.2 [(*M*+H)⁺, calcd C₂₀H₂₆F₃N₂O₂, 383.2]; LC/MS retention time (method B): *t*_R = 1.58 min.

Example 47

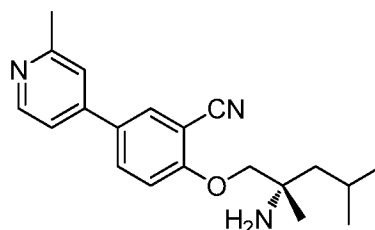
(*S*)-1-(4-(3-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



5 Prepared as described in Example 19. Obtained (*S*)-1-(4-(3-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amin (8.9 mg, 0.023 mmol, 25% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 2.6 Hz, 1H), 8.51 (d, *J* = 4.9 Hz, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.70 (dd, *J* = 7.1, 4.9 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 3.89 (q, *J* = 8.9 Hz, 2H),
 10 1.80 (dp, *J* = 12.7, 6.4 Hz, 1H), 1.40 (d, *J* = 5.5 Hz, 2H), 1.13 (s, 3H), 0.92 (dd, *J* = 6.6, 2.3 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -61.17, -133.88; LCMS (ESI) *m/e* 371.2 [(*M*+*H*)⁺, calcd C₁₉H₂₃F₄N₂O₁, 371.2]; LC/MS retention time (method B): *t*_R = 1.88 min.

15 Example 48

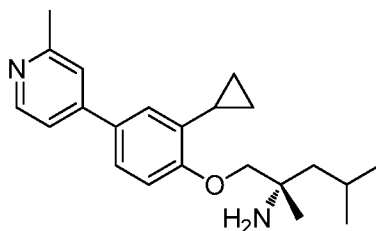
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile



Prepared as described in Example 19. Obtained (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile (39.4 mg, 0.116 mmol, 80% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.49 (d, *J* = 5.2 Hz, 1H), 8.23 (d, *J* = 2.4 Hz, 1H), 8.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.64 (s, 1H), 7.54 (dd, *J* = 5.3, 1.9 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 3.98 - 3.87 (m, 2H), 3.58 (s, 2H), 2.52 (s, 3H), 1.82 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.50 - 1.37 (m, 2H), 1.16 (s, 3H), 0.93 (dd, *J* = 6.6, 3.9 Hz, 6H); LCMS (ESI) *m/e* 324.1 [(*M*+*H*)⁺, calcd C₂₀H₂₆N₃O₁,
 25 324.2]; LC/MS retention time (method B): *t*_R = 1.46 min.

Example 49

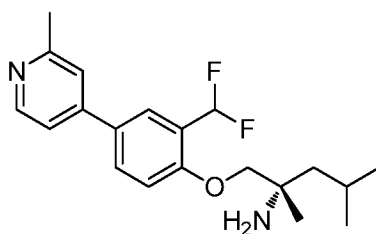
(*S*)-1-(2-cyclopropyl-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 19. Obtained (*S*)-1-(2-cyclopropyl-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (13.8 mg, 0.040 mmol, 41% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.42 (d, *J* = 5.3 Hz, 1H), 7.56 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.53 (s, 1H), 7.44 (d, *J* = 5.3 Hz, 1H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 3.77 (d, *J* = 2.2 Hz, 2H), 2.22 (ddd, *J* = 13.9, 8.4, 5.3 Hz, 1H), 1.82 (dq, *J* = 12.7, 6.4 Hz, 1H), 1.52 - 1.39 (m, 2H), 1.17 (s, 3H), 0.93 (t, *J* = 6.5 Hz, 8H), 0.77 (q, *J* = 4.3, 3.5 Hz, 2H). (2-Py-Me was likely buried in DMSO peak of 2.51); LCMS (ESI) *m/e* 339.1 [(*M*+*H*)⁺, calcd C₂₂H₃₁N₂O₁, 339.2]; LC/MS retention time (method B): *t*_R = 1.56 min.

Example 50

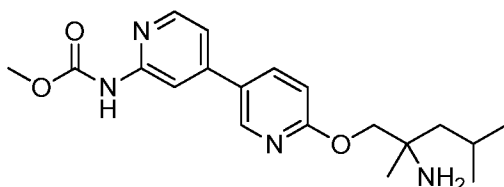
(*S*)-1-(2-(difluoromethyl)-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



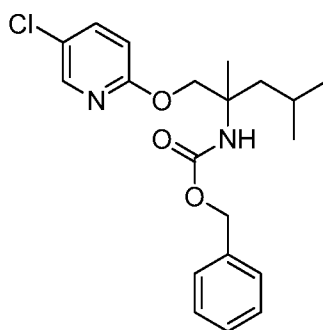
Prepared as described in Example 19. Obtained (*S*)-1-(2-(difluoromethyl)-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (22 mg, 0.061 mmol, 69% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 1H), 7.60 (s, 1H), 7.54 - 7.47 (m, 1H), 7.43 - 7.16 (m, 2H), 3.87 (s, 2H), 2.53 (s, 3H), 1.80 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.43 (qd, *J* = 14.1, 5.7 Hz, 2H), 1.16 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 349.0 [(*M*+*H*)⁺, calcd C₂₀H₂₇F₂N₂O₁, 349.2]; LC/MS retention time (method B): *t*_R = 1.47 min.

Example 51

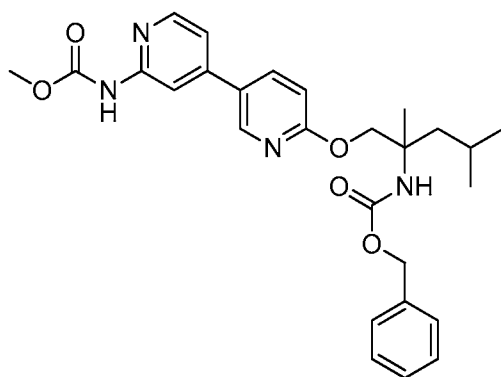
methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate



5 Prepared as described in Example 29.

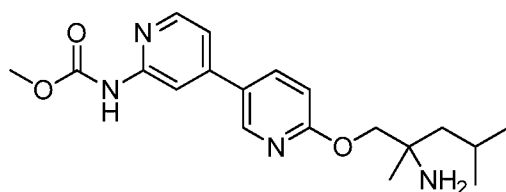
*Part A: Benzyl (1-((5-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

An NMP (0.3 mL) suspension of 5-chloropyridin-2-ol (0.023 g, 0.180 mmol),
 10 sodium carbonate (0.019 g, 0.180 mmol) and benzyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.0392 g, 0.120 mmol) was heated to 80 °C overnight. The reaction mixture was cooled to rt and diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified via silica
 15 gel chromatography (0-30% ethyl acetate in hexanes) to afford benzyl (1-((5-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.0387g, 0.103 mmol, 86%yield) as an off-white solid. ¹H NMR (400MHz, CHLOROFORM-d) δ 8.08 (d, J=2.3 Hz, 1H), 7.54 (dd, J=8.8, 2.8 Hz, 1H), 7.37 - 7.32 (m, 5H), 6.71 (d, J=8.8 Hz, 1H), 5.06 (s, 3H), 4.42 (d, J=10.5 Hz, 1H), 4.26 (d, J=10.8 Hz, 1H), 1.87 - 1.74 (m,
 20 2H), 1.72 - 1.63 (m, 1H), 1.43 (s, 3H), 0.96 (dd, J=6.3, 4.8 Hz, 6H); LCMS (ESI) *m/e* 377.3 [(M+H)⁺, calcd C₂₀H₂₆ClN₂O₃, 377.2]; LC/MS retention time (method A): *t_R* = 2.42 min.



Part B: Cbz methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate

- 5 A mixture of 2nd generation XPHOS precatalyst (1.587 mg, 2.017 μ mol), potassium phosphate tribasic (0.403 mL, 0.202 mmol), (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.020 g, 0.101 mmol) and benzyl (1-((5-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.038 g, 0.101 mmol) in THF (0.2 mL) was degassed via vacuum/ N₂ fill cycle three times.
- 10 The reaction mixture was heated at 70 °C overnight. The reaction was cooled to rt and diluted with ethyl acetate and washed with water (2X) followed by brine. The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated. The product was purified silica gel chromatography (50-100% ethyl acetate in hexanes) to afford Cbz methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate (0.011 g, 0.022 mmol, 22% yield) as a white solid. LCMS (ESI) *m/e* 493.3 [(M+H)⁺, calcd C₂₇H₃₃N₄O₅, 493.3]; LC/MS retention time (method B): *t_R* = 2.13 min.



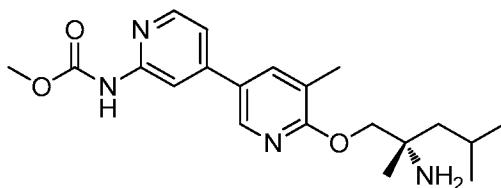
- 20 *Part C: methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate*

A mixture of Pd/C (5 mg, 4.70 μ mol) and Cbz methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate (0.011 g, 0.022 mmol) in ethanol (4 mL) was hydrogenated with a H₂ balloon at room temperature overnight.

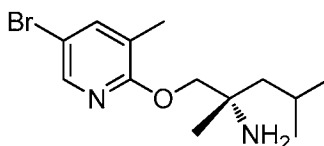
The reaction was filtered and washed with DCM. The filtrate was concentrated under reduced pressure and the residue was purified via reverse phase HPLC (acetonitrile/water/ 10 mM ammonium acetate) to afford methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate (6.6.mg, 0.018 mmol, 82% yield) as an off-white solid. ¹H NMR (600MHz, DMSO-d₆) δ 8.53 (s, 1H), 8.32 (d, *J*=5.1 Hz, 1H), 8.08 (s, 1H), 8.06 (dd, *J*=8.6, 2.0 Hz, 1H), 7.38 (d, *J*=5.1 Hz, 1H), 7.00 (d, *J*=8.4 Hz, 1H), 4.14 - 4.00 (m, 2H), 3.70 (s, 3H), 1.89 (s, 3H), 1.80 (dt, *J*=12.7, 6.1 Hz, 1H), 1.47 - 1.33 (m, 2H), 0.93 (d, *J*=6.6 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 3H); LCMS (ESI) *m/e* 359.3 [(M+H)⁺, calcd C₁₉H₂₇N₄O₃, 359.2]; LC/MS retention time (method B): *t*_R = 1.55 min.

Example 52

(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methyl-[3,4'-bipyridin]-2'-yl)carbamate

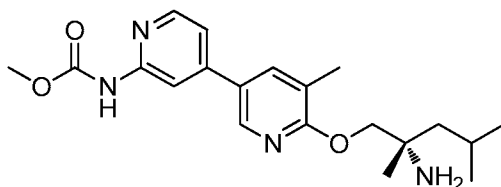


Prepared as in Example 51.



Part A: (*S*)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.

LCMS (ESI) *m/e* 323.1 [(M+Na)⁺, calcd C₁₃H₂₁BrN₂ONa, 323.1]; LC/MS retention time (method B): *t*_R = 1.96 min.



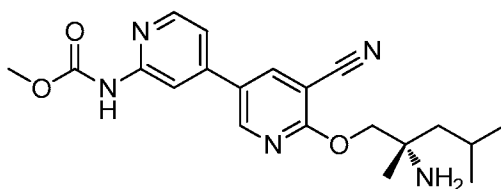
Part B: (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methyl-[3,4'-bipyridin]-2'-yl)carbamate.

A mixture of sodium carbonate (0.149 mL, 0.299 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (6.10 mg, 7.47 μ mol), (*S*)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.045 g, 0.149 mmol) and (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.029 g, 0.149 mmol) in dioxane (0.5 mL) (degassed with N₂) was heated at 80 °C for 5 h. The reaction was diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (acetonitrile/water/ 10 mM ammonium acetate to afford (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methyl-[3,4'-bipyridin]-2'-yl)carbamate (11.0 mg, 0.073 mmol, 20% yield) as an off-white solid. ¹H NMR (600MHz, DMSO-d₆) δ 10.25 (br. s., 1H), 8.35 (s, 1H), 8.31 (d, *J*=5.1 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.36 (d, *J*=5.1 Hz, 1H), 4.20 - 4.09 (m, 2H), 2.51 (br. s., 3H), 2.29 (s, 3H), 1.86 - 1.77 (m, 1H), 1.59 - 1.39 (m, 2H), 1.20 (d, *J*=5.1 Hz, 3H), 0.93 (d, *J*=6.6 Hz, 3H), 0.92 (d, *J*=6.6 Hz, 3H); LCMS (ESI) *m/e* 373.4 [(M+H)⁺, calcd C₂₀H₂₉N₄O₃ 373.2]; LC/MS retention time (method A): *t*_R = 1.89 min.

20

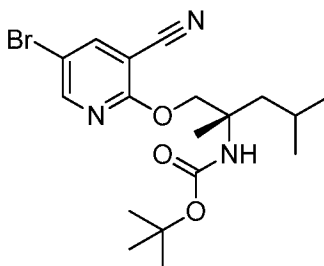
Example 53

(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate



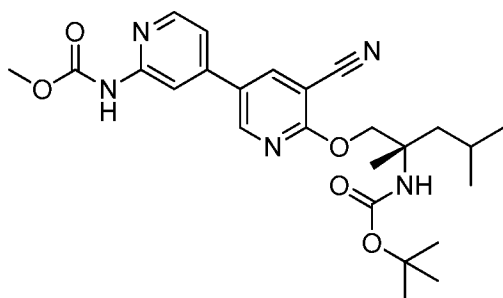
Prepared as in Example 51.

25



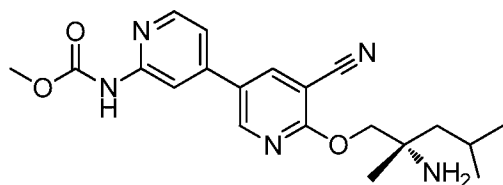
Part A: (*S*)-*tert*-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of sodium carbonate (0.246 g, 2.323 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.3408 g, 1.162 mmol) and 5-bromo-2-hydroxynicotinonitrile (0.277 g, 1.394 mmol) in DMF (4 mL) was heated at 80 °C overnight. The reaction was cooled to rt and diluted with ethyl acetate then washed with NaOH (1N) (2X) and water (1X). The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The product was purified silica gel chromatography (0-25% ethyl acetate in hexanes) to afford (*S*)-*tert*-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.261 g, 0.633 mmol, 55% yield) as a clear oil. LCMS (ESI) *m/e* 436.1 [(M+Na)⁺, calcd C₁₈H₂₆BrN₃O₃Na, 436.1]; LC/MS retention time (method B): *t*_R = 2.38 min.



Part B: Boc-(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate.

LCMS (ESI) *m/e* 484.4 [(M+H)⁺, calcd C₂₅H₃₄N₅O₅, 484.3]; LC/MS retention time (method A): *t*_R = 2.24 min.



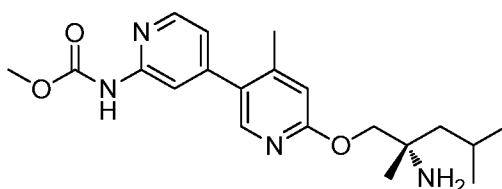
Part C: (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate.

Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate (13.3 mg, 0.034 mmol, 36% yield) as a white solid. ¹H

NMR (500MHz, DMSO- d_6) δ 10.36 (s, 1H), 8.81 - 8.77 (m, 1H), 8.68 - 8.63 (m, 1H), 8.36 (d, $J=5.1$ Hz, 1H), 8.09 (s, 1H), 7.43 (d, $J=4.0$ Hz, 1H), 4.20 (d, $J=5.9$ Hz, 2H), 3.71 (s, 3H), 3.39 (br. s., 2H), 1.82 (d, $J=6.2$ Hz, 1H), 1.40 (t, $J=5.5$ Hz, 2H), 1.14 (s, 3H), 0.95 - 0.90 (m, 6H); LCMS (ESI) m/e 367.2 [(M-NH $_2$), calcd C $_{20}$ H $_{23}$ N $_4$ O $_3$, 367.2]; LC/MS retention time (method B): t_R = 1.63 min.

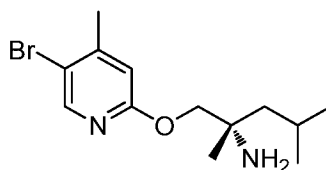
Example 54

(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate



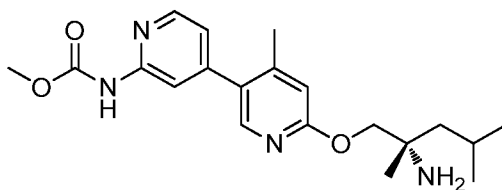
10

Prepared as in Example 51.



15 *Part A: (S)-1-((5-bromo-4-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.*

LCMS (ESI) m/e 301.2 [(M+H) $^+$], calcd C $_{13}$ H $_{22}$ BrN $_2$ O, 301.1]; LC/MS retention time (method A): t_R = 1.77 min.



20 *Part B: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate.*

Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate (15.3 mg, 0.041 mmol, 32% yield) as an off-white solid.

^{1} H NMR (500MHz, DMSO- d_6) δ 8.34 - 8.30 (m, 1H), 8.00 (s, 1H), 7.81 (s, 1H), 7.11 - 7.08 (m, 1H), 6.85 (s, 1H), 4.01 (d, $J=5.5$ Hz, 2H), 3.68 (s, 3H), 2.26 (s, 3H),

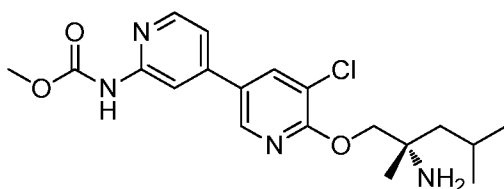
25

1.88 (s, 1H), 1.85 - 1.77 (m, 1H), 1.37 (s, 2H), 1.10 (s, 3H), 0.93 (m, 6H); LCMS (ESI) m/e 373.3 $[(M+H)^+]$, calcd $C_{20}H_{29}N_4O_3$, 373.2; LC/MS retention time (method B): t_R = 1.60 min.

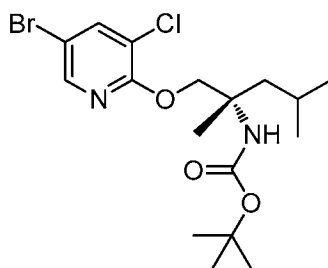
5

Example 55

(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate



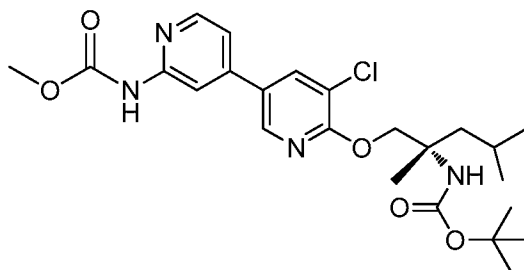
10 Prepared as in Example 51.



Part A: (S)-tert-butyl (1-((5-bromo-3-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

15 ^1H NMR (400MHz, CHLOROFORM- d) δ 8.07 (d, J =2.3 Hz, 1H), 7.76 (d, J =2.3 Hz, 1H), 4.65 (br. s., 1H), 4.48 (d, J =10.3 Hz, 1H), 4.32 (d, J =10.3 Hz, 1H), 1.90 - 1.75 (m, 2H), 1.67 - 1.53 (m, 1H), 1.41 (s, 9H), 1.39 (s, 3H), 0.99 (d, J =2.0 Hz, 3H), 0.97 (d, J =2.0 Hz, 3H); LCMS (ESI) m/e 443.1 $[(M+Na)^+]$, calcd $C_{17}H_{26}BrClN_2O_3Na$, 443.1; LC/MS retention time (method B): t_R = 2.55 min.

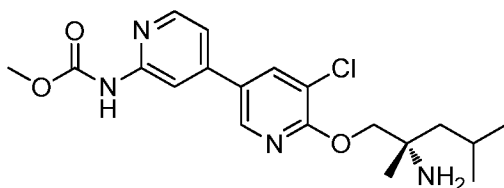
20



Part B: Boc-(S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate.

LCMS (ESI) m/e 493.4 [(M+H)⁺, calcd C₂₄H₃₄ClN₄O₅, 493.2]; LC/MS retention time (method A): t_R = 2.38 min.

5



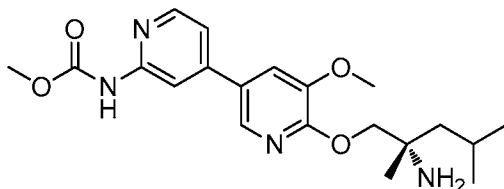
Part C: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate.

Obtained (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate (19.6 mg, 0.047 mmol, 85% yield) as an off-white solid.
¹H NMR (500MHz, DMSO-d₆) δ 8.49 (d, J =2.2 Hz, 1H), 8.34 (d, J =5.1 Hz, 1H), 8.25 (d, J =2.2 Hz, 1H), 8.07 (s, 1H), 7.42 (dd, J =5.1, 1.5 Hz, 1H), 4.22 - 4.06 (m, 2H), 3.71 (s, 3H), 1.87 - 1.75 (m, 1H), 1.48 - 1.34 (m, 2H), 1.14 (s, 3H), 0.93 (d, J =3.7 Hz, 3H), 0.92 (d, J =3.7 Hz, 3H); LCMS (ESI) m/e 393.3 [(M+H)⁺, calcd C₁₉H₂₆ClN₄O₃, 393.2]; LC/MS retention time (method A): t_R = 1.98 min.

15

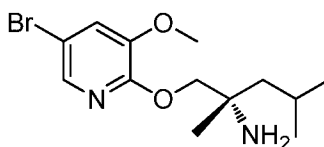
Example 56

(S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methoxy-[3,4'-bipyridin]-2'-yl)carbamate



20

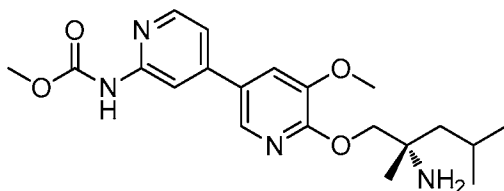
Prepared as in Example 51.



25

Part A: (*S*)-1-((5-bromo-3-methoxypyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.

LCMS (ESI) m/e 338.9 $[(M+Na)^+]$, calcd $C_{13}H_{21}BrN_2O_2Na$, 339.1]; LC/MS retention time (method B): t_R = 1.87 min.



5

Part B: (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methoxy-[3,4'-bipyridin]-2'-yl)carbamate.

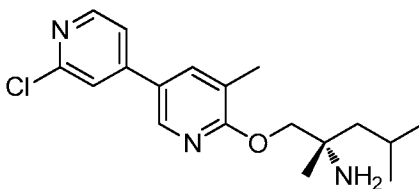
Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methoxy-[3,4'-bipyridin]-2'-yl)carbamate (8.4 mg, 0.021 mmol, 29% yield) as an off-white solid.

10 ^1H NMR (500MHz, DMSO- d_6) δ 8.32 (d, J =5.1 Hz, 1H), 8.09 (s, 1H), 8.04 (d, J =1.8 Hz, 1H), 7.56 (d, J =1.5 Hz, 1H), 7.41 (d, J =4.0 Hz, 1H), 4.08 (q, J =10.3 Hz, 2H), 3.92 (s, 3H), 3.70 (s, 3H), 3.45 (br. s., 3H), 1.81 (dt, J =13.0, 6.3 Hz, 1H), 1.47 - 1.31 (m, 2H), 1.12 (s, 3H), 0.92 (m, 6H); LCMS (ESI) m/e 389.1 $[(M+H)^+]$, calcd $C_{20}H_{29}N_4O_4$, 389.2]; LC/MS retention time (method B): t_R = 1.64 min.

15

Example 57

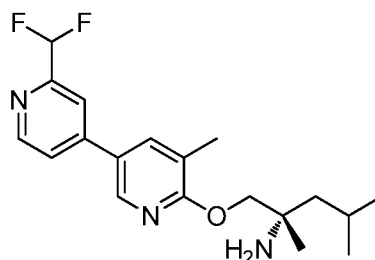
(*S*)-1-((2'-chloro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as in Example 51. Obtained (*S*)-1-((2'-chloro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (15 mg, 0.044 mmol, 49% yield) as an off-white solid. ^1H NMR (600MHz, DMSO- d_6) δ 8.51 (br. s., 1H), 8.44 (d, J =5.1 Hz, 1H), 8.09 (br. s., 1H), 7.87 (s, 1H), 7.76 (d, J =4.0 Hz, 1H), 4.10 - 4.04 (m, 2H), 2.26 (s, 3H), 1.84 - 1.75 (m, 1H), 1.40 (t, J =6.2 Hz, 2H), 1.13 (s, 3H), 0.92 (t, J =6.4 Hz, 6H); LCMS (ESI) m/e 334.3 $[(M-NH_2)^+]$, calcd $C_{18}H_{25}ClN_3O$, 334.2];
 25 LC/MS retention time (method B): t_R = 1.94 min.

Example 58

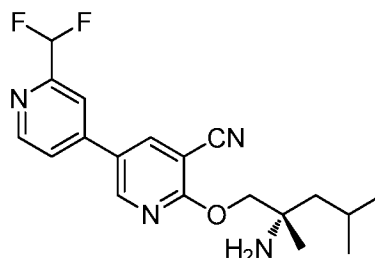
(*S*)-1-((2'-(difluoromethyl)-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



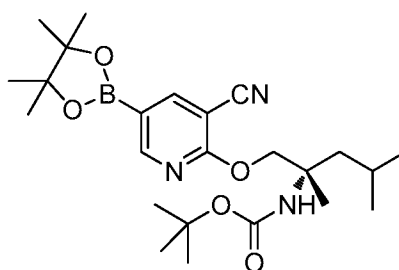
- 5 Prepared as in Example 51. Obtained (*S*)-1-((2'-(difluoromethyl)-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (15.1 mg, 0.043 mmol, 81% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.72 (d, J = 5.2 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.01 (s, 1H), 7.92 (d, J = 5.2 Hz, 1H), 6.99 (t, J = 54.9 Hz, 1H), 4.16 - 4.02 (m, 2H), 2.28 (s, 3H), 1.80 (tt, J =
- 10 11.5, 5.7 Hz, 1H), 1.49 - 1.35 (m, 2H), 1.14 (s, 3H), 0.92 (m, 6H); LCMS (ESI) m/e 350.3 $[(M+H)^+]$, calcd $\text{C}_{19}\text{H}_{26}\text{F}_2\text{N}_3\text{O}$, 350.2]; LC/MS retention time (method A): t_R = 1.80 min.

Example 59

- 15 (*S*)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-(difluoromethyl)-[3,4'-bipyridine]-5-carbonitrile

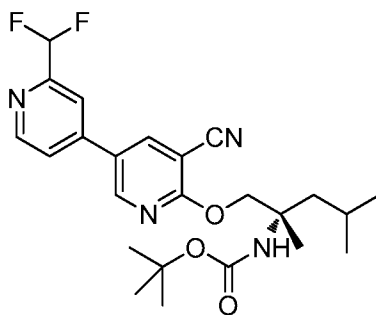


Prepared as in Example 51.



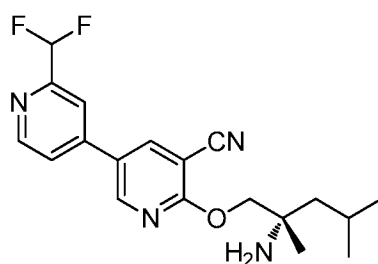
Part A: (S)-tert-butyl (1-((3-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

To a 20 mL vial was added (*S*)-*tert*-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (73 mg, 0.177 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (54.0 mg, 0.212 mmol), and potassium acetate (52.1 mg, 0.531 mmol) in dioxane (2 mL) with nitrogen bubbling to give a colorless suspension. PdCl₂(dppf) (3.89 mg, 5.31 μmol) was added under nitrogen. The vial was sealed and the mixture was heated at 80 °C for 4 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude material was used directly in the next step.



Part B: (S)-tert-butyl (1-((5-cyano-2'-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

The mixture of (*S*)-*tert*-butyl (1-((3-cyano-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.040 g, 0.088 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloromethane complex (5.03 mg, 6.16 μmol), 4-chloro-2-(difluoromethyl)pyridine hydrochloride (0.018 g, 0.088 mmol) and Na₂CO₃ (0.176 mL, 0.352 mmol) in dioxane (1 mL) (degassed with N₂) was heated at 120 °C for 16 h. The reaction mixture was cooled to rt, diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was directly carried onto next reaction. LCMS (ESI) *m/e* 483.2 [(M+Na)⁺, calcd C₂₄H₃₀F₂N₄NaO₃, 483.2]; LC/MS retention time (method B): *t*_R = 2.30 min.



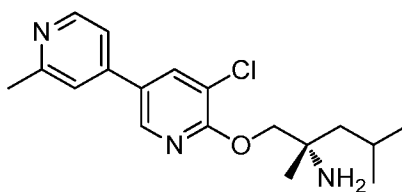
Part C: (S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-(difluoromethyl)-[3,4'-bipyridine]-5-carbonitrile.

Prepared using procedure described in Example 51 to afford (S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-(difluoromethyl)-[3,4'-bipyridine]-5-carbonitrile (4.7 mg, 0.013 mmol, 15% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.02 (d, *J* = 2.5 Hz, 1H), 8.95 (d, *J* = 2.6 Hz, 1H), 8.80 (d, *J* = 5.1 Hz, 1H), 8.15 (s, 1H), 8.02 (d, *J* = 5.0 Hz, 1H), 7.01 (t, *J* = 54.8 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 1.86 (dq, *J* = 12.4, 6.2 Hz, 1H), 1.79 (dd, *J* = 14.4, 5.5 Hz, 1H), 1.62 (dd, *J* = 14.3, 5.5 Hz, 1H), 1.41 (s, 3H), 0.98 (dd, *J* = 6.7, 2.2 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -73.65; LCMS (ESI) *m/e* 383.3 [(M+Na)⁺, calcd C₁₉H₂₂F₂N₄NaO₁, 383.2]; LC/MS retention time (method B): *t_R* = 1.77 min.

15

Example 60

(S)-1-((5-chloro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine

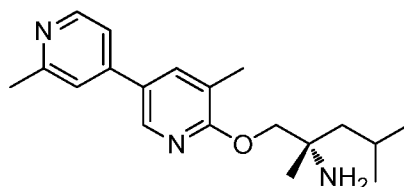


Prepared as in Example 51. Obtained (S)-1-((5-chloro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (2 mg, 5.99 μmol, 31% yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 8.59 (d, *J*=1.8 Hz, 1H), 8.50 (d, *J*=5.1 Hz, 1H), 8.39 (d, *J*=1.8 Hz, 1H), 7.67 (s, 1H), 7.57 (d, *J*=4.4 Hz, 1H), 4.19 - 4.10 (m, 2H), 2.53 (s, 3H), 1.86 - 1.77 (m, 1H), 1.47 - 1.37 (m, 2H), 1.15 (s, 3H), 0.99 - 0.88 (m, 6H); LCMS (ESI) *m/e* 334.3 [(M+H)⁺, calcd C₁₈H₂₅ClN₃O, 334.2]; LC/MS retention time (method A): *t_R* = 1.90 min.

25

Example 61

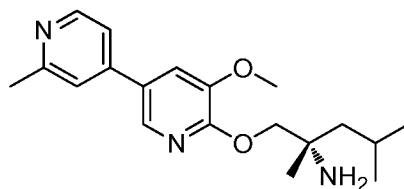
(*S*)-1-((2',5-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as in Example 51. Obtained (*S*)-1-((5-chloro-2'-methyl-[3,4'-
 5 bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (20.5 mg, 0.065 mmol, 41% yield)
 as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.47 (d, $J=5.1$ Hz, 1H), 8.43
 (d, $J=2.2$ Hz, 1H), 8.01 (s, 1H), 7.59 (s, 1H), 7.50 (d, $J=5.5$ Hz, 1H), 4.11 - 4.00 (m,
 2H), 2.52 (s, 3H), 2.26 (s, 3H), 1.80 (dq, $J=12.6, 6.3$ Hz, 1H), 1.46 - 1.35 (m, 2H),
 1.13 (s, 3H), 0.93 (d, $J=4.8$ Hz, 3H), 0.92 (d, $J=4.8$ Hz, 3H); LCMS (ESI) m/e 297.1
 10 [(M-NH $_2$) $^+$, calcd C $_{19}$ H $_{25}$ ClN $_2$ O, 297.2]; LC/MS retention time (method B): t_R = 1.51
 min.

Example 62

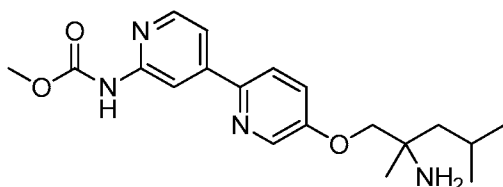
(*S*)-1-((5-methoxy-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



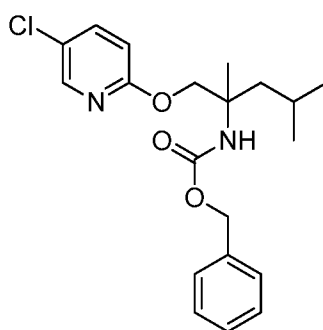
Prepared as in Example 51. Obtained (*S*)-1-((5-methoxy-2'-methyl-[3,4'-
 15 bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (20.5 mg, 0.065 mmol, 41% yield)
 as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.48 (d, $J=5.1$ Hz, 1H), 8.14
 (s, 1H), 7.65 (d, $J=4.0$ Hz, 2H), 7.55 (d, $J=3.7$ Hz, 1H), 4.06 (q, $J=10.1$ Hz, 2H), 3.93
 20 (s, 3H), 2.53 (s, 3H), 1.85 - 1.70 (m, 1H), 1.42 - 1.31 (m, 2H), 1.11 (s, 3H), 0.92 (t,
 $J=7.0$ Hz, 6H); LCMS (ESI) m/e 330.1 [(M+H) $^+$, calcd C $_{19}$ H $_{28}$ N $_3$ O $_2$, 330.2]; LC/MS
 retention time (method B): t_R = 1.42 min.

Example 63

methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate



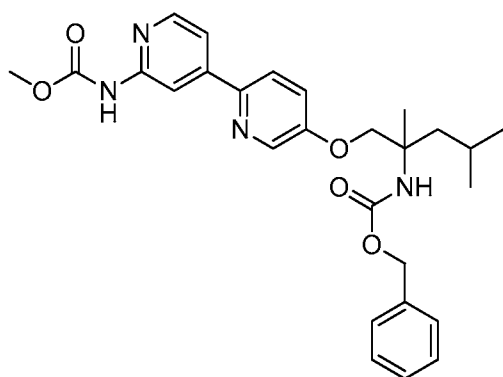
5 Prepared as in Example 29.



Part A: Benzyl (1-((5-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

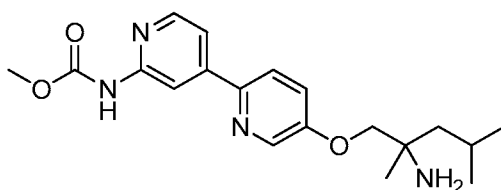
LCMS (ESI) m/e 377.3 $[(M+H)^+]$, calcd $C_{20}H_{26}ClN_2O_3$, 377.2]; LC/MS

10 retention time (method A): t_R = 2.42 min.



Part B: Cbz methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate.

15 LCMS (ESI) m/e 493.0 $[(M+H)^+]$, calcd $C_{27}H_{33}N_4O_5$, 493.2]; LC/MS retention time (method B): t_R = 2.15 min.

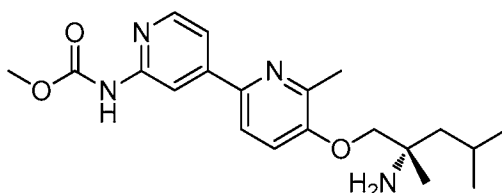


Part C: methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate

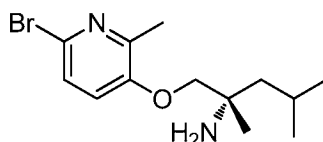
A mixture of Pd/C (4 mg, 3.76 μ mol) and Cbz protected methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate (0.0123 g, 0.025 mmol) in ethanol (4 mL) was stirred under H₂ balloon at room temperature overnight. The reaction mixture was filtered and the flask was rinsed with CH₂Cl₂. The filter cake was washed with CH₂Cl₂. The filtrate was concentrated under reduced pressure and the residue was purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate (12.1 mg, 0.032 mmol, 98% yield) as an off-white solid. ¹H NMR (600MHz, DMSO-d₆) δ 10.14 (br. s., 1H), 8.49 (s, 1H), 8.45 (d, *J*=2.8 Hz, 1H), 8.32 (d, *J*=5.1 Hz, 1H), 7.97 (d, *J*=8.8 Hz, 1H), 7.63 (d, *J*=5.1 Hz, 1H), 7.54 (dd, *J*=8.7, 2.8 Hz, 1H), 3.84 (s, 2H), 3.71 (s, 3H), 1.82 (tt, *J*=12.7, 6.5 Hz, 1H), 1.46 - 1.35 (m, 2H), 1.14 (s, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.6 Hz, 3H); LCMS (ESI) *m/e* 359.3 [(M+H)⁺, calcd C₁₉H₂₇N₄O₃, 359.2]; LC/MS retention time (method A): *t*_R = 1.48 min.

Example 64

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

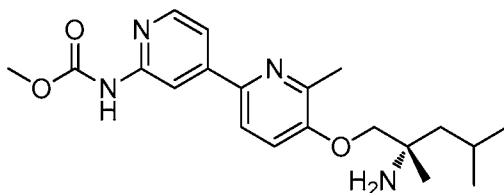


Prepared as in Example 19.



Part A: (*S*)-1-((6-bromo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine.

LCMS (ESI) m/e 284.2 [(M-NH₂)⁺, calcd C₁₃H₁₉BrNO, 284.1]; LC/MS retention time (method A): t_R = 1.78 min (SM: t_R = 1.61 min).



5

Part B: (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate.

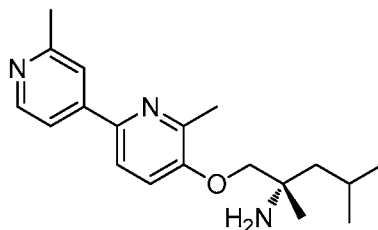
Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate (8.5 mg, 0.022 mmol, 34% yield) as an off-white solid. .

10 ¹H NMR (500 MHz, DMSO-d₆) δ 8.48 (s, 1H), 8.30 (d, J = 5.3 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.43 (d, J = 8.6 Hz, 1H), 3.79 (d, J = 2.0 Hz, 2H), 3.58 (s, 3H), 2.50 (s, 3H), 1.79 (m, 1H), 1.51 - 1.34 (m, 2H), 1.16 (s, 3H), 0.93 (t, J = 6.4 Hz, 6H); LCMS (ESI) m/e 373.3 [(M+H)⁺, calcd C₂₀H₂₉N₄O₃, 373.2]; LC/MS retention time (method A): t_R = 1.82 min.

15

Example 65

(*S*)-1-((2',6-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

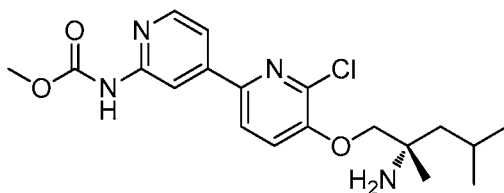


Prepared as in Example 51. Obtained ((*S*)-1-((2',6-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (7.2 mg, 0.022 mmol, 29% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.49 (d, J = 5.3 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 7.78 (d, J = 5.3 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 3.78 (s, 2H), 2.54 (s, 3H), 2.51 (s, 3H), 1.83 (dt, J = 12.8, 6.4 Hz, 1H), 1.42 (t, J = 5.2 Hz, 2H), 1.15 (s, 3H), 0.94 (t, J = 6.2 Hz, 6H); LCMS (ESI) m/e 314.4 [(M+H)⁺, calcd C₁₉H₂₈N₃O, 314.2]; LC/MS retention time (method A): t_R = 1.84 min.

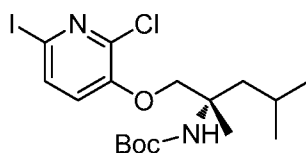
25

Example 66

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate

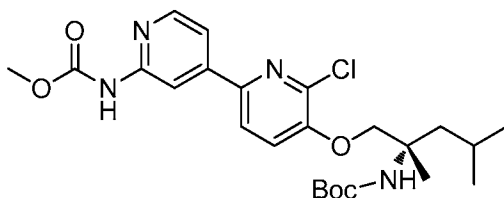


5 Prepared as in Example 32.



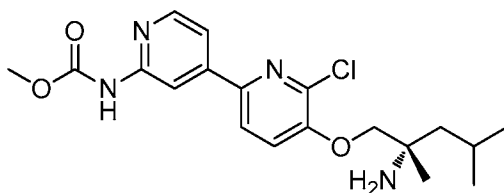
Part A: (*S*)-tert-butyl (1-((2-chloro-6-iodopyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 490.9 $[(M+Na)^+]$, calcd $C_{17}H_{26}ClIN_2NaO_3$, 491.1]; LC/MS retention time (method B): t_R = 2.40 min.



Part B: (*S*)-methyl (5-((2-Boc-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate.

15 LCMS (ESI) m/e 493.0 $[(M+H)^+]$, calcd $C_{24}H_{34}ClN_4O_5$, 493.2]; LC/MS retention time (method B): t_R = 2.19 min.



Part C: (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate.

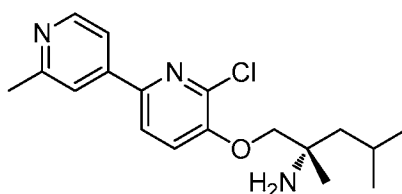
Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate (12.6 mg, 0.032 mmol, 69% yield) as an off-white solid.

- 5 ¹H NMR (500 MHz, DMSO-d₆) δ 8.45 (s, 1H), 8.35 (d, *J* = 5.3 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 5.2 Hz, 1H), 3.93 (s, 2H), 3.71 (s, 3H), 1.81 (dq, *J* = 13.1, 6.5 Hz, 1H), 1.45 (qd, *J* = 14.0, 5.5 Hz, 2H), 1.18 (s, 3H), 0.93 (t, *J* = 6.4 Hz, 6H); LCMS (ESI) *m/e* 393.0 [(M+H)⁺, calcd C₁₉H₂₆ClN₄O₃, 393.2]; LC/MS retention time (method A): *t*_R = 1.66 min.

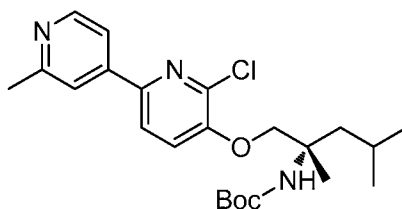
10

Example 67

(*S*)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

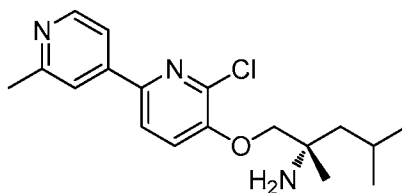


- 15 Prepared as in Example 32.



Part A: (*S*)-tert-butyl (1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

- 20 Synthesis followed previous procedure. LCMS (ESI) *m/e* 434.0 [(M+H)⁺, calcd C₂₃H₃₃ClN₃O₃, 434.2]; LC/MS retention time (method B): *t*_R = 1.96 min.



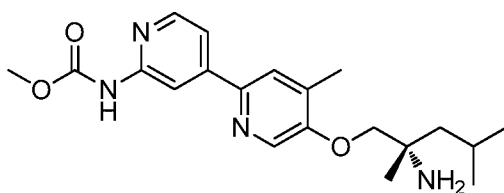
Part B: (*S*)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine.

Obtained (*S*)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (4.6 mg, 0.013 mmol, 30% yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.53 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.76 (d, *J* = 5.3 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 2H), 2.55 (s, 3H), 1.82 (p, *J* = 6.4 Hz, 1H), 1.52 - 1.38 (m, 2H), 1.17 (s, 3H), 0.94 (t, *J* = 6.3 Hz, 6H); LCMS (ESI) *m/e* 334.1 [(M+H)⁺, calcd C₁₈H₂₅ClN₃O₁, 334.2]; LC/MS retention time (method A): *t*_R = 1.48 min.

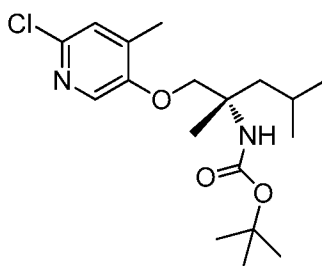
10

Example 68

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate

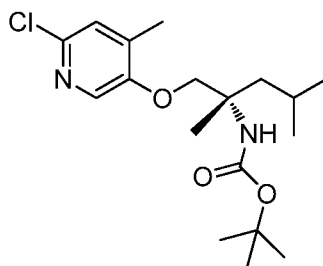


15 Prepared as in Example 32.



Part A: (*S*)-tert-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

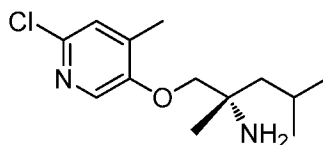
20 LCMS (ESI) *m/e* 357.3 [(M+H)⁺, calcd C₁₈H₃₀ClN₂O₃, 357.2]; LC/MS retention time (method A): *t*_R = 2.23 min.



Part B: (S)-tert-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) m/e 357.3 $[(M+H)^+]$, calcd $C_{18}H_{30}ClN_2O_3$, 357.2]; LC/MS

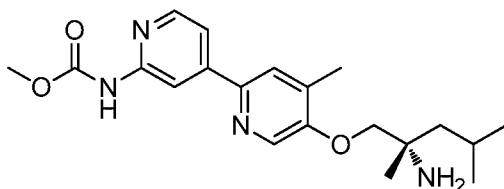
5 retention time (method A): t_R = 2.23 min.



Part C: (S)-1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine.

LCMS (ESI) m/e 257.0 $[(M+H)^+]$, calcd $C_{13}H_{22}ClN_2O$, 257.1]; LC/MS

10 retention time (method B): t_R = 1.70 min.



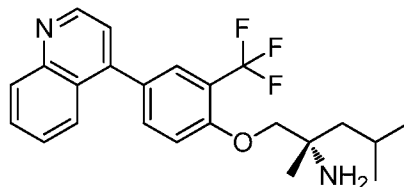
Part D: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate.

15 Obtained (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate (1.1 mg, 2.92 μ mol, 5% yield) as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.49 (s, 1H), 8.36 (s, 1H), 8.32 (d, J =5.1 Hz, 1H), 7.87 (s, 1H), 7.63 (d, J =5.5 Hz, 1H), 3.89 (s, 2H), 3.71 (s, 3H), 2.32 (s, 3H), 1.86 - 1.79 (m, 1H), 1.42 (t, J =5.7 Hz, 2H), 1.15 (s, 3H), 0.93 (t, J =6.6 Hz, 6H) ; LCMS

20 (ESI) m/e 373.1 $[(M+H)^+]$, calcd $C_{20}H_{29}N_4O_3$, 373.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 69

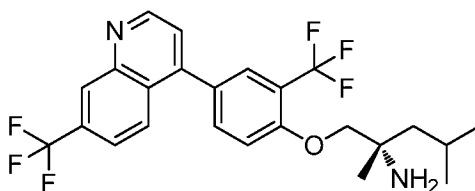
(*S*)-2,4-dimethyl-1-(4-(quinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine



Prepared as in Example 32. Obtained (*S*)-2,4-dimethyl-1-(4-(quinolin-4-yl)-
 2-(trifluoromethyl)phenoxy)pentan-2-amine (50 mg, 0.123 mmol, 17% yield) as a
 brown solid. ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.96 (d, $J=4.5$ Hz, 1H), 8.20
 (d, $J=8.5$ Hz, 1H), 7.87 (dd, $J=8.4$, 0.9 Hz, 1H), 7.75 (td, $J=4.2$, 1.4 Hz, 2H), 7.65
 (dd, $J=8.5$, 2.0 Hz, 1H), 7.58 - 7.52 (m, 1H), 7.33 (d, $J=4.5$ Hz, 1H), 7.14 (d, $J=8.5$
 Hz, 1H), 3.93 - 3.86 (m, 2H), 1.82 (d, $J=6.5$ Hz, 1H), 1.68 - 1.59 (m, 2H), 1.54 (t,
 10 $J=5.5$ Hz, 2H), 1.28 (s, 3H), 1.06 - 0.98 (m, 6H); ^{19}F NMR (376 MHz,
 CHLOROFORM-*d*) δ -62.29 (s, 3F); LCMS (ESI) m/e 403.2 [(*M*+*H*) $^+$, calcd
 C₂₃H₂₆F₃N₂O, 403.2]; LC/MS retention time (method B): t_R = 1.73 min.

Example 70

(*S*)-2,4-dimethyl-1-(2-(trifluoromethyl)-4-(7-(trifluoromethyl)quinolin-4-
 yl)phenoxy)pentan-2-amine

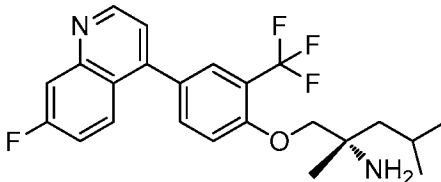


Prepared as in Example 32. A mixture of 2-(dicyclohexylphosphino)-
 2',4',6'-triisopropylbiphenyl (2.90 mg, 6.09 μmol), potassium acetate (0.090 g, 0.913
 20 mmol), 2nd generation Xphos precatalyst (2.395 mg, 3.04 μmol), 4-chloro-8-
 (trifluoromethyl)quinoline (0.0705 g, 0.304 mmol) and hypodiboric acid (0.041 g,
 0.457 mmol) in ethanol (4 mL) was degassed three times via vacuum/N₂ fill cycle.
 The reaction mixture was heated at 80 °C for 3 h. The reaction was cooled to room
 temperature. (*S*)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-
 25 amine (0.026 g, 0.073 mmol) and 2nd generation Xphos precatalyst (2.395 mg, 3.04
 μmol) in THF (4 mL) was added to the reaction mixture, followed by addition of
 potassium phosphate tribasic (3 mL, 1.500 mmol) at room temperature. The reaction

mixture was underwent vacuum/N₂ fill cycle three times before heated at 80 °C overnight. The reaction was cooled to rt then diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The crude was purified by reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate to afford (*S*)-2,4-dimethyl-1-(2-(trifluoromethyl)-4-(7-(trifluoromethyl)quinolin-4-yl)phenoxy)pentan-2-amine (8.9 mg, 0.018 mmol, 5%yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 9.11 (d, *J*=4.3 Hz, 1H), 8.46 (s, 1H), 8.08 (d, *J*=8.5 Hz, 1H), 7.90 (d, *J*=8.9 Hz, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.83 (s, 1H), 7.70 (d, *J*=4.3 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 1H), 3.94 - 3.87 (m, 2H), 1.82 (d, *J*=6.1 Hz, 1H), 1.42 (d, *J*=5.5 Hz, 2H), 1.15 (s, 3H), 0.94 (dd, *J*=6.4, 2.1 Hz, 6H); LCMS (ESI) *m/e* 471.3 [(M+H)⁺, calcd C₂₄H₂₅F₆N₂O, 471.2]; LC/MS retention time (method A): *t*_R = 2.28 min.

Example 71

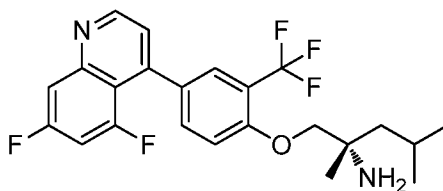
(*S*)-1-(4-(7-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



Prepared as in Example 32. Obtained (*S*)-1-(4-(7-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (4.2 mg, 9.89 umol, 2%yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 8.96 (d, *J*=4.0 Hz, 1H), 7.97 - 7.79 (m, 3H), 7.77 (s, 1H), 7.60 - 7.53 (m, 1H), 7.50 (d, *J*=4.0 Hz, 1H), 7.43 (d, *J*=8.5 Hz, 1H), 3.89 (d, *J*=7.6 Hz, 2H), 1.81 (d, *J*=6.4 Hz, 1H), 1.41 (d, *J*=5.2 Hz, 2H), 1.14 (s, 3H), 0.93 (d, *J*=4.9 Hz, 6H); LCMS (ESI) *m/e* 404.2 [(M-NH₂)⁺, calcd C₂₃H₂₂F₄NO, 404.2]; LC/MS retention time (method B): *t*_R = 1.88 min.

Example 72

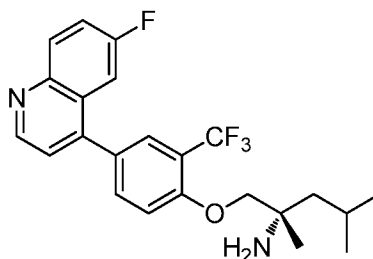
(*S*)-1-(4-(5,7-difluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



5 Prepared as in Example 32. Obtained (*S*)-1-(4-(5,7-difluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (17.5 mg, 0.039 mmol, 23%yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 9.02 - 8.96 (m, 1H), 7.82 - 7.76 (m, 1H), 7.73 (br. s., 2H), 7.56 (br. s., 1H), 7.46 (d, *J*=4.3 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 1H), 3.88 (d, *J*=6.4 Hz, 2H), 1.82 (br. s., 1H), 1.42 (d, *J*=5.2 Hz, 2H), 1.15 (s, 3H), 0.93 (d, *J*=6.6 Hz, 6H); LCMS (ESI) *m/e* 439.4 [(*M*+*H*)⁺, calcd C₂₃H₂₄F₅N₂O, 439.2]; LC/MS retention time (method A): *t*_R = 2.14 min.

Example 73

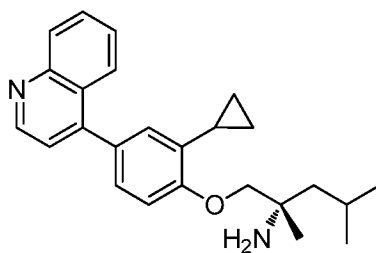
(*S*)-1-(4-(6-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



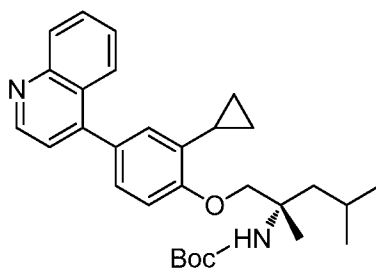
15 Prepared as in Example 32. Obtained (*S*)-1-(4-(6-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (9.6 mg, 0.023 mmol, 22%yield) as an off-white solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.95 (d, *J* = 4.4 Hz, 1H), 8.21 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 2.6 Hz, 1H), 7.75 (td, *J* = 8.9, 2.9 Hz, 1H), 7.57 (d, *J* = 4.4 Hz, 1H), 7.50 (dd, *J* = 10.3, 3.0 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 3.92 (q, *J* = 8.9 Hz, 2H), 1.83 (dt, *J* = 13.1, 6.7 Hz, 1H), 1.43 (d, *J* = 5.5 Hz, 2H), 1.16 (s, 3H), 0.94 (dd, *J* = 6.7, 3.2 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -61.01, -244.69; LCMS (ESI) *m/e* 421.2 [(*M*+*H*)⁺, calcd C₂₃H₂₅F₄N₂O₁, 421.2]; LC/MS retention time (method B): *t*_R = 1.80 min.

Example 74

(S)-1-(2-cyclopropyl-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

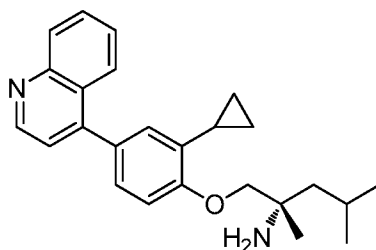


5 Prepared as in Example 32.



Part A: (S)-tert-butyl (1-(2-cyclopropyl-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 475.1 $[(M+H)^+]$, calcd $C_{30}H_{39}N_2O_3$, 475.3]; LC/MS retention time (method B): t_R = 2.21 min.



Part B: (S)-1-(2-cyclopropyl-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine.

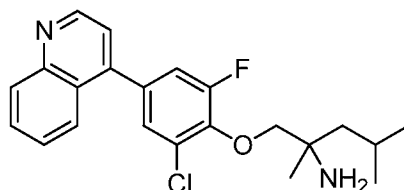
15 Obtained (12.7 mg, 0.032 mmol, 33%yield) as an off-white solid. ^1H NMR (500 MHz, $DMSO-d_6$) δ 8.90 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 4.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 7.03 (s, 1H), 3.82 (s, 2H), 2.27 (p, J = 6.9 Hz, 1H), 1.85 (dt, J = 12.7, 6.6 Hz, 1H), 1.47 (q, J = 8.2, 7.0 Hz, 2H), 1.20 (s, 3H), 0.95 (q, J = 7.9, 7.2 Hz, 8H), 0.71 (t, J = 4.1 Hz, 2H); LCMS

20

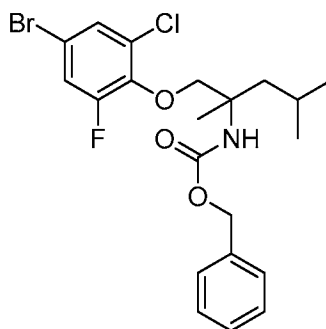
(ESI) m/e 375.1 $[(M+H)^+]$, calcd $C_{25}H_{31}N_2O_1$, 375.2]; LC/MS retention time (method B): t_R = 1.69 min.

Example 75

5 1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



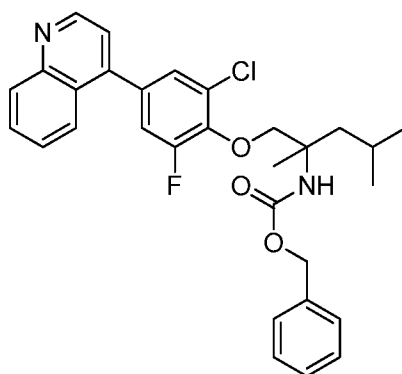
Prepared as in Example 29.



10

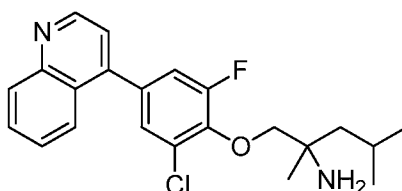
Part A: Benzyl (1-(4-bromo-2-chloro-6-fluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate.

An NMP (0.3 mL) suspension of 4-bromo-2-chloro-6-fluorophenol (23.00 mg, 0.102 mmol), sodium carbonate (35 mg, 0.330 mmol) and benzyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.0334 g, 0.102 mmol) was
 15 heated at 50 °C overnight. The reaction was diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was carried on without further purification. LCMS (ESI) m/e 496.0 $[(M+Na)^+]$, calcd $C_{21}H_{24}ClBrFNO_3Na$,
 20 494.1]; LC/MS retention time (method B): t_R = 2.59 min.



Part B: Benzyl (1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) m/e 521.4 $[(M+H)^+]$, calcd $C_{30}H_{31}ClFN_2O_3$, 521.2; LC/MS
 5 retention time (method A): t_R = 2.38 min.



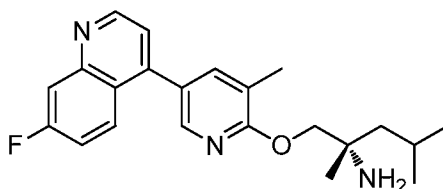
Part C: 1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

Triethylsilane(0.1 ml, 0.626 mmol) was added to a CH_2Cl_2 (0.2 mL)
 10 suspension of palladium(II) acetate(2 mg, 8.91 μ mol) and triethylamine(0.1 ml, 0.717 mmol) at rt. The reaction turned black. The solution was stirred at room temperature for 10 min before addition of CH_2Cl_2 (0.2 mL) solution of benzyl (1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.0441 g, 0.085 mmol) (the flask contain the benzyl (1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.0441 g, 0.085 mmol) was rinsed
 15 with CH_2Cl_2 (0.2 mL) and added to the reaction mixture). The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude material was purified via reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford 1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (8.9 mg, 0.022 mmol, 26% yield.) ^1H NMR (500MHz,
 20 DMSO- d_6) δ 8.96 (d, J =4.4 Hz, 1H), 8.13 (d, J =8.4 Hz, 1H), 7.88 (s, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.60 - 7.50 (m, 3H), 3.98 - 3.90 (m, 2H), 1.89 - 1.81 (m, 1H), 1.44 (dd, J =14.9, 5.7 Hz, 2H), 1.18 (s, 3H), 0.97 (dd, J =9.4, 6.8 Hz, 6H); LCMS (ESI)

m/e 387.2 $[(M+H)^+]$, calcd $C_{22}H_{25}FCIN_2O$, 387.2]; LC/MS retention time (method B): t_R = 1.70 min.

Example 76

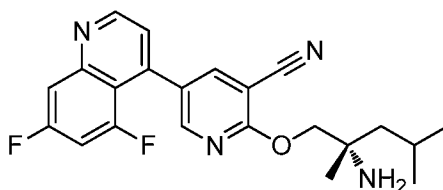
5 (S)-1-((5-(7-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



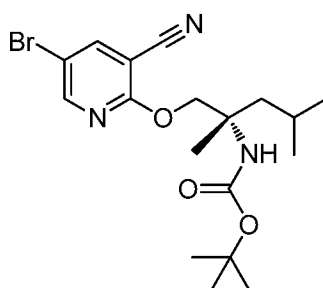
Intermediates prepared as described in Example 19. A mixture of potassium acetate (0.026 g, 0.266 mmol), (S)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0267 g, 0.089 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.027 g, 0.106 mmol) in dioxane (1 mL) underwent vacuum/backfill N_2 (5X). $PdCl_2(dppf)$ (1.946 mg, 2.66 μ mol) was added to the reaction mixture and the reaction was heated at 80 °C overnight. The reaction mixture was cooled to room temperature. $PdCl_2(dppf)$ (3.26 mg, 4.45 μ mol), sodium carbonate (0.089 mL, 0.178 mmol, 2N), 4-chloro-7-fluoroquinoline (16.16 mg, 0.089 mmol) and (S)-2,4-dimethyl-1-((3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)pentan-2-amine (31.0 mg, 0.089 mmol) in dioxane (1.2 mL) were added to the vessel mixture and the mixture was degassed via vacuum/ N_2 fill cycle three times. The reaction mixture was heated at 130 °C for 4 h. The reaction was cooled to rt then diluted with ethyl acetate and washed with water (2X) followed by brine. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude was purified via reverse phase HPLC (acetonitrile/water/10 mM ammonium acetate) to afford (S)-1-((5-(7-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (15.2 mg, 0.041 mmol, 47% yield) as an off-white solid. ^1H NMR (500MHz, $DMSO-d_6$) δ 8.99 - 8.95 (m, 1H), 8.20 - 8.16 (m, 1H), 7.98 (dd, $J=9.2, 6.2$ Hz, 1H), 7.88 - 7.83 (m, 1H), 7.81 (s, 1H), 7.59 - 7.53 (m, 1H), 7.49 (d, $J=4.4$ Hz, 1H), 4.11 (d, $J=4.4$ Hz, 2H), 3.46 (br. s., 2H), 1.90 (s, 3H), 1.87 - 1.79 (m, 1H), 1.45 (t, $J=6.2$ Hz, 2H), 1.17 (s, 3H), 0.95 (t, $J=6.1$ Hz, 6H); LCMS (ESI) m/e 386.2 $[(M+H)^+]$, calcd $C_{22}H_{27}FN_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 77

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5,7-difluoroquinolin-4-yl)nicotinonitrile

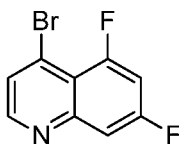


5 Prepared as in Example 53.



Part A: (S)-tert-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 434.1 $[(M+Na)^+]$, calcd $C_{18}H_{26}BrN_3O_3Na$, 434.1]; LC/MS retention time (method B): t_R = 2.38 min.

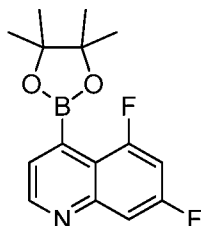


Part B: 4-bromo-5,7-difluoroquinoline

15 To a 20 mL microwave tube was added 4-chloro-5,7-difluoroquinoline (0.159 g, 0.795 mmol) and propionitrile (1mL), followed by TMS-Br (0.206 mL, 1.59 mmol) at room temperature. A precipitate formed. The tube was sealed and heated to 100°C overnight. The reaction was cooled to room temperature. The crude mixture was poured into iced NaOH (1N, 3 mL) and the tube was washed with water.

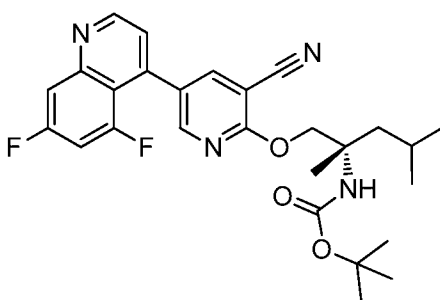
20 The aqueous layer was extracted with diethyl ether (3X). The diethyl ether layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give 4-bromo-5,7-difluoroquinoline (14.2 mg, 0.582 mmol, 73% yield) as a yellow

solid. LCMS (ESI) m/e 243.8 $[(M+Na)^+]$, calcd $C_9H_5BrNF_2$, 244.0]; LC/MS retention time (method B): t_R = 2.04 min.



5 *Part C: 5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline*

A mixture of potassium acetate (0.122 g, 1.242 mmol), 4-bromo-5,7-difluoroquinoline (0.1010 g, 0.414 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.126 g, 0.497 mmol) in dioxane (3 mL) underwent a cycle of vacuum/backfill with nitrogen 5 times. $PdCl_2(dppf)$ (9.09 mg, 0.012 mmol) was
 10 added to the reaction mixture at room temperature and the reaction was heated at 80 °C overnight. The crude was used as it is in the next step.

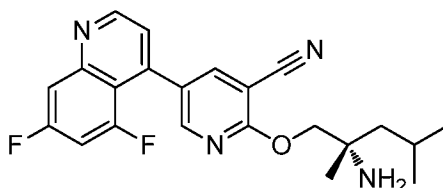


15 *Part D: (S)-tert-butyl (1-((3-cyano-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

A mixture of sodium carbonate (0.138 mL, 0.276 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (7.89 mg, 9.66 μ mol), 5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.040 g, 0.138 mmol) and (S)-tert-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.057 g, 0.138 mmol) in dioxane (2
 20 mL) (degassed) was heated at 100 °C for 3 h. The reaction was diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0-10-25% ethyl acetate in hexanes) to afford (S)-tert-butyl (1-

((3-cyano-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.0372g, 0.075 mmol, 54% yield) as a brown solid. LCMS (ESI) m/e 519.0 $[(M+Na)^+]$, calcd $C_{27}H_{30}F_2N_4O_3Na$, 519.2]; LC/MS retention time (method B): $t_R = 2.38$ min.

5



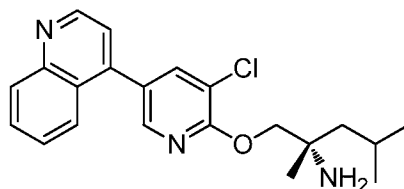
Part E: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5,7-difluoroquinolin-4-yl)nicotinonitrile.

^1H NMR (500MHz, DMSO- d_6) δ 9.04 (d, $J=4.4$ Hz, 1H), 8.59 (s, 1H), 8.54 (br. s., 1H), 7.82 (d, $J=9.2$ Hz, 1H), 7.70 - 7.59 (m, 1H), 7.54 (d, $J=4.4$ Hz, 1H), 4.30 - 4.17 (m, 2H), 3.44 (br. s., 2H), 1.87 - 1.79 (m, 1H), 1.50 - 1.36 (m, 2H), 1.16 (s, 3H), 0.96 (d, $J=2.9$ Hz, 3H), 0.94 (d, $J=2.9$ Hz, 3H); LCMS (ESI) m/e 397.2 $[(M+H)^+]$, calcd $C_{22}H_{23}F_2N_4O$, 397.2]; LC/MS retention time (method B): $t_R = 2.39$ min.

15

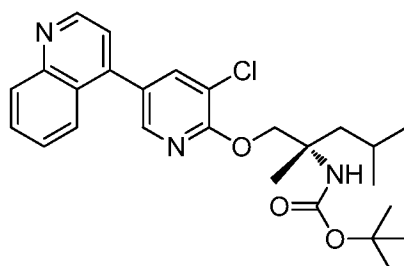
Example 78

(S)-1-((3-chloro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as in example 77.

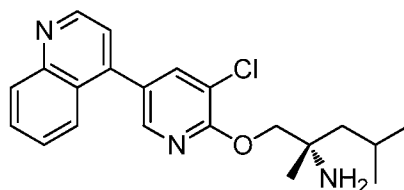
20



Part A: Boc (S)-1-((3-chloro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.

(ESI) m/e 470.4 $[(M+H)^+]$, calcd $C_{26}H_{33}ClN_3O_3$, 470.2]; LC/MS retention time (method A): t_R = 2.45 min.

5



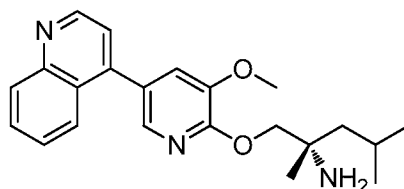
Part B: (S)-1-((3-chloro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.

^1H NMR (500MHz, DMSO- d_6) δ 8.99 (d, J =4.4 Hz, 1H), 8.36 (d, J =1.8 Hz, 1H), 8.25 (d, J =1.8 Hz, 1H), 7.96 (s, 1H), 7.89 - 7.80 (m, 2H), 7.67 (t, J =7.5 Hz, 1H), 7.55 (d, J =4.4 Hz, 1H), 4.59 - 4.42 (m, 2H), 1.94 - 1.61 (m, 3H), 1.43 (s, 3H), 0.98 (t, J =6.4 Hz, 6H); LCMS (ESI) m/e 370.3 $[(M+H)^+]$, calcd $C_{21}H_{25}ClN_3O$, 370.2]; LC/MS retention time (method A): t_R = 2.09 min.

15

Example 79

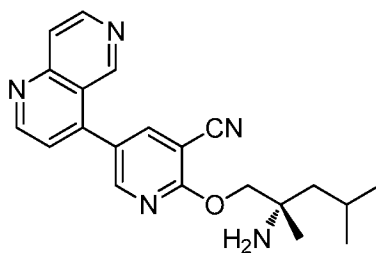
(S)-1-((3-methoxy-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



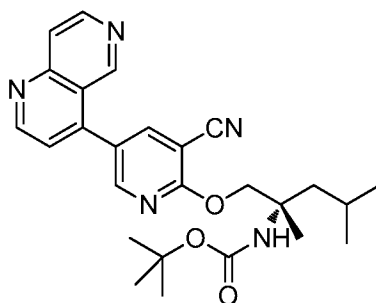
Prepared as in Example 77. Obtained (S)-1-((3-methoxy-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (5.4 mg, 0.014 mmol, 23%yield) as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.96 (d, J =4.4 Hz, 1H), 8.12 (d, J =8.4 Hz, 1H), 7.97 (d, J =8.4 Hz, 1H), 7.86 (d, J =1.5 Hz, 1H), 7.82 (t, J =7.5 Hz, 1H), 7.64 (t, J =7.7 Hz, 1H), 7.53 (d, J =4.4 Hz, 1H), 7.51 (d, J =1.5 Hz, 1H), 4.17 - 4.06 (m, 2H), 3.60 (br. s., 3H), 1.84 (dt, J =12.8, 6.4 Hz, 1H), 1.47 - 1.36 (m, 2H), 1.15 (s, 3H), 0.95 (t, J =7.2 Hz, 6H); LCMS (ESI) m/e 366.0 $[(M+H)^+]$, calcd $C_{22}H_{28}N_3O_2$, 366.2]; LC/MS retention time (method B): t_R = 1.55 min.

25

Example 80

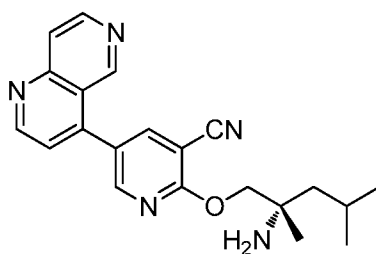
(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)nicotinonitrile

5 Prepared as in Example 77.



Part A: (S)-tert-butyl (1-((3-cyano-5-(1,6-naphthyridin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

10 LCMS (ESI) m/e 484.2 $[(M+Na)^+]$, calcd $C_{26}H_{31}F_2N_5Na_1O_3$, 484.2]; LC/MS retention time (method B): t_R = 2.14 min.



15 *Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)nicotinonitrile.*

Obtained *(S)*-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)nicotinonitrile (22 mg, 0.058 mmol, 66% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.28 (s, 1H), 9.23 (d, J = 4.4 Hz, 1H), 8.84 (d, J = 5.7 Hz, 1H), 8.78 (d, J = 2.4 Hz, 1H), 8.75 (d, J = 2.5 Hz, 1H), 8.04 (d, J = 5.8 Hz, 1H), 7.74 (d, J = 4.5 Hz, 1H), 4.68 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 1.89 (dq, J

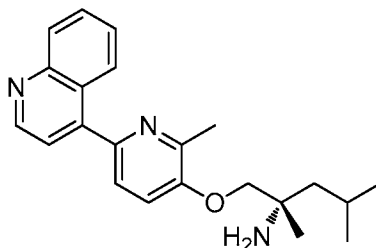
20

= 12.7, 6.2 Hz, 1H), 1.81 (dd, $J = 14.4, 5.5$ Hz, 1H), 1.64 (dd, $J = 14.4, 5.6$ Hz, 1H), 1.44 (s, 3H), 1.01 (d, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e 362.2 $[(M+H)^+]$, calcd $C_{21}H_{24}N_5O_1$, 362.2]; LC/MS retention time (method B): $t_R = 1.56$ min.

5

Example 81

(*S*)-2,4-dimethyl-1-((2-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine

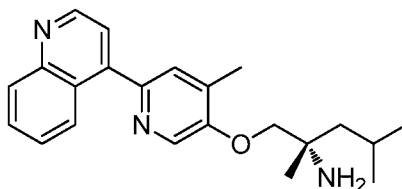


Prepared as in Example 77. Obtained (*S*)-2,4-dimethyl-1-((2-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine (10.3 mg, 0.028 mmol, 43%yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.96 (d, $J = 4.4$ Hz, 1H), 8.25 (d, $J = 8.5$ Hz, 1H), 8.10 (d, $J = 8.5$ Hz, 1H), 7.79 (t, $J = 7.6$ Hz, 1H), 7.65 - 7.56 (m, 3H), 7.51 (d, $J = 8.4$ Hz, 1H), 3.81 (d, $J = 2.2$ Hz, 2H), 2.53 (s, 3H), 1.84 (dq, $J = 12.6, 6.4$ Hz, 1H), 1.50 - 1.38 (m, 2H), 1.17 (s, 3H), 0.96 (t, $J = 6.2$ Hz, 6H); LCMS (ESI) m/e 350.3 $[(M+H)^+]$, calcd $C_{22}H_{28}N_3O_1$, 350.2]; LC/MS retention time (method A): $t_R = 1.86$ min.

15

Example 82

(*S*)-2,4-dimethyl-1-((4-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine

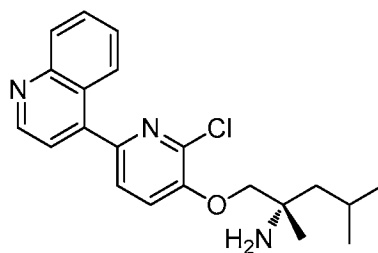


20

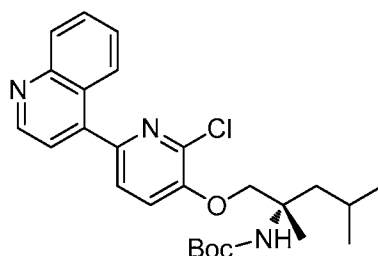
Prepared as in Example 77. Obtained (*S*)-2,4-dimethyl-1-((4-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine (11 mg, 0.030 mmol, 39%yield) as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.97 (d, $J=4.4$ Hz, 1H), 8.44 (s, 1H), 8.25 (d, $J=8.8$ Hz, 1H), 8.10 (d, $J=8.4$ Hz, 1H), 7.80 (t, $J=7.7$ Hz, 1H), 7.67 - 7.57 (m, 3H), 3.94 (s, 2H), 2.34 (s, 3H), 1.87 - 1.81 (m, 1H), 1.52 - 1.40 (m, 2H), 1.18 (s, 3H), 0.96 (t, $J=6.8$ Hz, 6H); LCMS (ESI) m/e 350.1 $[(M+H)^+]$, calcd $C_{22}H_{28}N_3O$, 350.2]; LC/MS retention time (method B): $t_R = 1.67$ min.

25

Example 83

(S)-1-((2-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

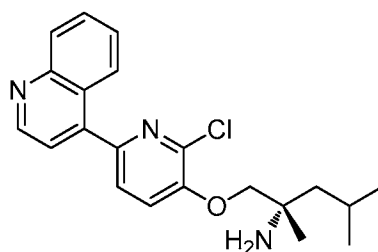
5 Prepared as in Example 77.



Part A: (S)-tert-butyl (1-((2-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) m/e 470.0 $[(M+H)^+]$, calcd $C_{26}H_{33}ClN_3O_3$, 470.2; LC/MS

10 retention time (method B): t_R = 2.15 min.



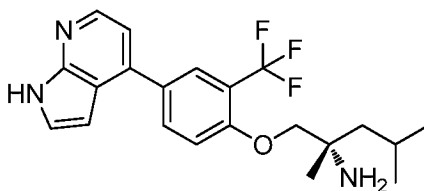
Part B: (S)-1-((2-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

15 Obtained (6.3 mg, 0.016 mmol, 36%yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.00 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 8.5 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.86 - 7.77 (m, 3H), 7.69 - 7.60 (m, 2H), 3.97 - 3.87 (m, 2H), 1.85 (dt, J = 12.8, 6.5 Hz, 1H), 1.44 (t, J = 4.8 Hz, 2H), 1.17 (s, 3H), 0.96 (t, J = 6.0 Hz, 6H); LCMS (ESI) m/e 370.0 $[(M+H)^+]$, calcd $C_{21}H_{25}ClN_3O_1$, 370.2; LC/MS retention time (method B): t_R = 1.57 min.

20

Example 84

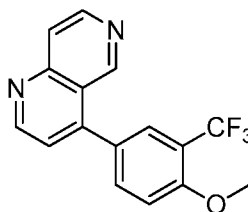
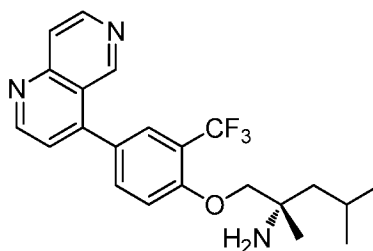
(*S*)-1-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



5 Prepared as in example 19 to obtain (*S*)-1-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (27 mg, 0.069 mmol, 79% yield) as an off-white solid. ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.36 (d, *J*=5.0 Hz, 1H), 8.00 (d, *J*=2.0 Hz, 1H), 7.89 (dd, *J*=8.5, 2.0 Hz, 1H), 7.41 (d, *J*=3.5 Hz, 1H), 7.18 - 7.08 (m, 2H), 6.68 (d, *J*=3.5 Hz, 1H), 3.92 - 3.84 (m, 2H), 1.82 - 1.77 (m, 1H), 1.60 - 1.48 (m, 2H), 1.28 (s, 3H), 1.01 (dd, *J*=9.0, 6.8 Hz, 6H); ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -62.31 (s, 3F); LCMS (ESI) *m/e* 392.2 [(*M*+*H*)⁺, calcd C₂₁H₂₅F₃N₃O, 392.2]; LC/MS retention time (method B): *t_R* = 1.81 min.

Example 85

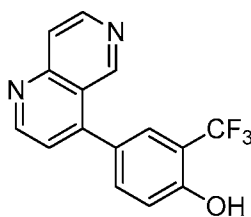
15 (*S*)-1-(4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



20 *Part A: 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine.*

To a 20 mL vial was added 4-chloro-1,6-naphthyridine (200 mg, 1.215 mmol), (4-methoxy-3-(trifluoromethyl)phenyl)boronic acid (321 mg, 1.458 mmol), and potassium phosphate tribasic (4.86 mL, 2.430 mmol) in THF (2.5 mL) to give a

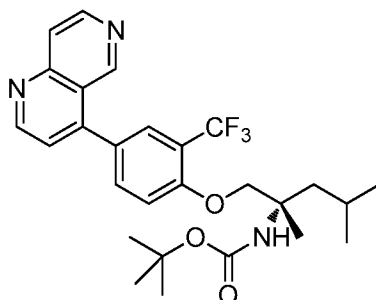
yellow suspension. After degassing with N₂ for 5 min, 2nd generation XPHOS precatalyst (19.12 mg, 0.024 mmol) was added. The mixture was sealed under nitrogen and heated at 40 °C for 2 h. The reaction mixture was cooled to rt and diluted with water and EtOAc. The layers were separated. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (up to 8% MeOH/CH₂Cl₂) to afford 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine (369 mg, 1.213 mmol, quantitative yield) as a light yellow solid: ¹H NMR (400 MHz, Chloroform-d) δ 9.37 (d, *J* = 0.9 Hz, 1H), 9.14 (d, *J* = 4.5 Hz, 1H), 8.83 (d, *J* = 5.9 Hz, 1H), 8.03 (dd, *J* = 6.0, 0.9 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.47 (d, *J* = 4.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 4.05 (s, 3H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -62.63; LCMS (ESI) *m/e* 305.2 [(M+H)⁺, calcd C₁₆H₁₂F₃N₂O₁, 305.1]; LC/MS retention time (method A): *t*_R = 1.86 min.



Part B: 4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenol

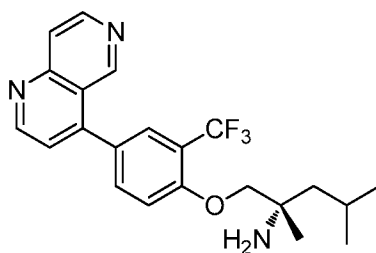
To a 250 mL round-bottomed flask was added 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine (369 mg, 1.213 mmol) in CH₂Cl₂ (5 mL) under nitrogen to give a yellow solution. BBr₃ (12.13 mL, 12.13 mmol) was slowly added. The mixture was refluxed under nitrogen for 5 h. The reaction was slowly quenched with 1N NaOH to adjust the pH to ~5. EtOAc was added. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (up to 8% MeOH/CH₂Cl₂) to afford 4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenol (124 mg, 0.427 mmol, 35%) as a white solid: ¹H NMR (400 MHz, Chloroform-d) δ 9.45 (s, 1H), 9.21 (d, *J* = 4.7 Hz, 1H), 8.84 (d, *J* = 6.1 Hz, 1H), 8.16 (d, *J* = 6.1 Hz, 1H), 7.89 - 7.75 (m, 1H), 7.60 (q, *J* = 3.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 1H); ¹⁹F NMR

(376 MHz, Chloroform-d) δ -62.58; LCMS (ESI) m/e 291.2 $[(M+H)^+]$, calcd $C_{15}H_{10}F_3N_2O_1$, 291.2]; LC/MS retention time (method B): t_R = 1.59 min.



5 *Part C: (S)-tert-butyl (1-(4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.*

LCMS (ESI) m/e 526.2 $[(M+Na)^+]$, calcd $C_{27}H_{32}F_3N_3Na_1O_3$, 526.2]; LC/MS retention time (method B): t_R = 2.31 min.



10

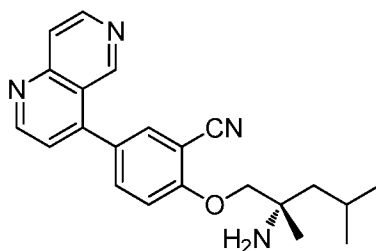
Part D: (S)-1-(4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine.

Obtained (35.7 mg, 0.087 mmol, 99% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO-d₆) δ 9.26 (s, 1H), 9.17 (d, J = 4.5 Hz, 1H), 8.80 (d, J = 5.8 Hz, 1H), 8.01 (d, J = 5.9 Hz, 1H), 7.95 (d, J = 8.7 Hz, 1H), 7.90 (s, 1H), 7.69 (d, J = 4.4 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 3.94 (q, J = 9.0 Hz, 2H), 1.83 (dq, J = 12.9, 6.4 Hz, 1H), 1.44 (dd, J = 5.8, 2.6 Hz, 2H), 1.17 (s, 3H), 0.94 (dd, J = 6.8, 3.3 Hz, 6H); ^{19}F NMR (376 MHz, DMSO-d₆) δ -61.02; LCMS (ESI) m/e 404.2 $[(M+H)^+]$, calcd $C_{22}H_{25}F_3N_3O_1$, 362.2]; LC/MS retention time (method B): t_R = 1.79 min.

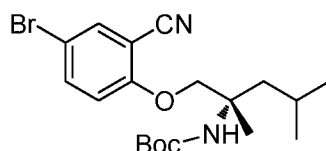
20

Example 86

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile

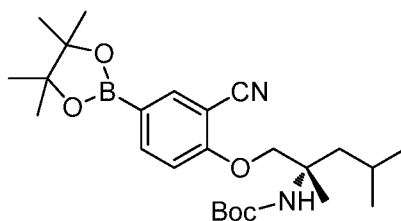


5 Prepared as in Example 51.



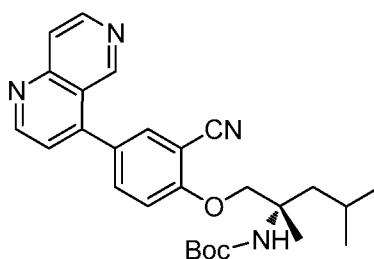
Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate.

- 10 ^1H NMR (400 MHz, Chloroform- d) δ 7.63 (d, J = 2.5 Hz, 1H), 7.58 (dd, J = 9.0, 2.5 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 4.57 (s, 1H), 4.31 (d, J = 9.0 Hz, 1H), 4.09 (d, J = 9.0 Hz, 1H), 1.90 (dd, J = 14.0, 6.5 Hz, 1H), 1.86 - 1.75 (m, 1H), 1.47 (dd, J = 14.0, 5.0 Hz, 1H), 1.39 (s, 3H), 1.37 (s, 9H), 0.99 (d, J = 1.9 Hz, 3H), 0.97 (d, J = 1.9 Hz, 3H); LCMS (ESI) m/e 432.9 $[(M+Na)^+]$, calcd $C_{19}H_{27}BrN_2NaO_3$, 433.1];
- 15 LC/MS retention time (method B): t_R = 2.38 min.



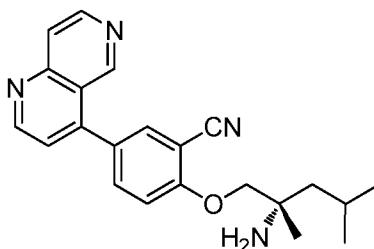
Part B: (S)-tert-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

- 20 LCMS (ESI) m/e 481.1 $[(M+Na)^+]$, calcd $C_{25}H_{39}BN_2NaO_5$, 481.3]; LC/MS retention time (method B): t_R = 2.49 min.



Part C: (S)-tert-butyl (1-(2-cyano-4-(1,6-naphthyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) m/e 483.1 $[(M+Na)^+]$, calcd $C_{27}H_{32}N_4NaO_3$, 483.2]; LC/MS
 5 retention time (method B): t_R = 2.10 min.

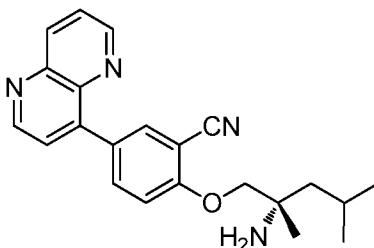


Part D: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile.

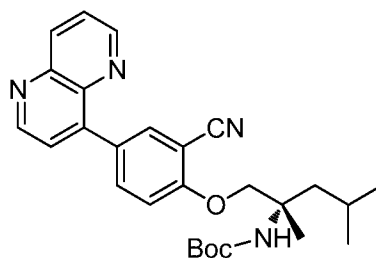
10 Obtained (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile (6.7 mg, 0.017 mmol, 34% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.27 (s, 1H), 9.17 (d, J = 4.5 Hz, 1H), 8.80 (d, J = 5.8 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H), 8.01 (d, J = 5.8 Hz, 1H), 7.97 (dd, J = 8.7, 2.3 Hz, 1H), 7.67 (d, J = 4.5 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 4.03 - 3.92 (m, 2H), 1.85 (dt, J =
 15 12.6, 6.3 Hz, 1H), 1.51 - 1.40 (m, 2H), 1.18 (s, 3H), 0.96 (dd, J = 6.7, 4.3 Hz, 6H); LCMS (ESI) m/e 361.0 $[(M+H)^+]$, calcd $C_{22}H_{25}N_4O$, 361.2]; LC/MS retention time (method B): t_R = 1.58 min.

Example 87

20 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,5-naphthyridin-4-yl)benzonitrile

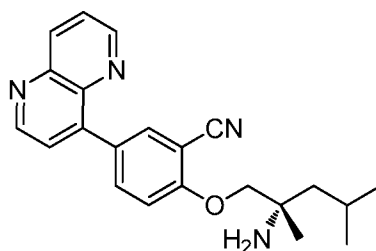


Prepared as in Example 51.



Part A: (S)-tert-butyl (1-(2-cyano-4-(1,5-naphthyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) m/e 483.1 $[(M+Na)^+]$, calcd $C_{27}H_{32}N_4NaO_3$, 483.2; LC/MS retention time (method B): t_R = 2.22 min.



Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,5-naphthyridin-4-yl)benzonitrile.

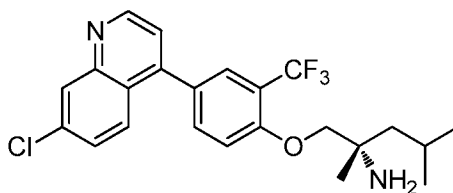
Obtained (5.5 mg, 0.015 mmol, 29% yield) as an off-white solid. ^1H NMR (500 MHz, DMSO- d_6) δ 9.06 (t, J = 4.6 Hz, 2H), 8.51 (d, J = 8.4 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.18 - 8.11 (m, 1H), 7.90 - 7.82 (m, 2H), 7.41 (d, J = 8.9 Hz, 1H), 3.65 (s, 2H), 1.84 (dt, J = 12.4, 6.5 Hz, 1H), 1.45 (dd, J = 5.6, 2.5 Hz, 2H), 1.17 (s, 3H), 0.95 (dd, J = 6.7, 3.9 Hz, 6H). (OCH₂ was likely buried in a broad peak); LCMS (ESI) m/e 361.0 $[(M+H)^+]$, calcd $C_{22}H_{25}N_4O$, 361.2; LC/MS retention time (method B): t_R = 1.68 min.

20

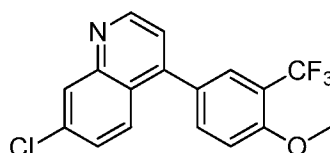
25

Example 88

(*S*)-1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



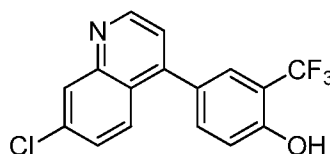
5



Part A: 7-chloro-4-(4-methoxy-3-(trifluoromethyl)phenyl)quinoline

A mixture of 4,7-dichloroquinoline (810 mg, 4.09 mmol), (4-methoxy-3-(trifluoromethyl)phenyl)boronic acid (900 mg, 4.09 mmol), PdCl₂(dppf) (150 mg, 0.205 mmol), cesium carbonate (2000 mg, 6.14 mmol), and 1,4-dioxane (10 mL) were charged to a 20 mL pressure rated vial and a stream of nitrogen was bubbled through for 10 minutes. The vial was sealed, purged of oxygen, and stirred at 90 °C overnight. The resultant mixture was vacuum filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel chromatography (5-40 % ethyl acetate/hexanes gradient elution) to afford 7-chloro-4-(4-methoxy-3-(trifluoromethyl)phenyl)quinoline (1.04 g, 3.08 mmol, 75% yield) as a white solid. The material was carried on without further purification. LCMS (ESI) *m/e* 338.1 [(M+H)⁺, calcd C₁₇H₁₂ClF₃NO, 338.1]; LC/MS retention time (method D): *t_R* = 1.13 min.

20

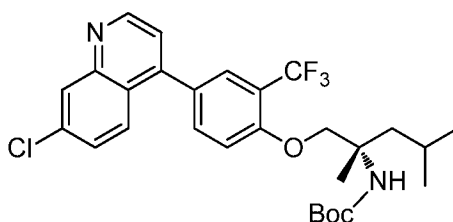


Part B: 4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenol

A solution of 7-chloro-4-(4-methoxy-3-(trifluoromethyl)phenyl)quinoline (0.51 g, 1.510 mmol) in dichloromethane (10 mL) 0 °C was treated with BBr₃ (3.02 mL, 3.02 mmol). The cooling bath was removed and the reaction solution stirred at ambient temperature overnight. The resultant was cooled to 0 °C and quenched with

25

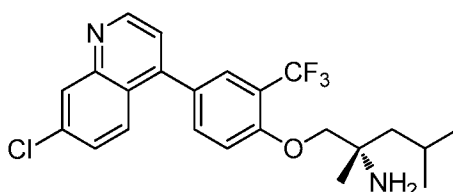
saturated aqueous sodium bicarbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x10 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give an orange solid. The crude residue was adsorbed onto silica gel and purified by silica
 5 gel chromatography (10-80 % ethyl acetate/hexanes) to afford 4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenol (195 mg, 0.271 mmol, 18% yield) as a pale yellow solid. LCMS (ESI) m/e 323.9 $[(M+H)^+]$, calcd $C_{16}H_{10}ClF_3NO$, 324.0]; LC/MS retention time (method D): t_R = 1.00 min.



10

Part C: (S)-tert-butyl (1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenol (195 mg, 0.602 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate
 15 2,2-dioxide (194 mg, 0.663 mmol), cesium carbonate (393 mg, 1.205 mmol), and *N,N*-dimethylformamide (4 mL) was heated to 80 °C overnight. The resultant mixture was cooled to room temperature and diluted with ethyl acetate (40 mL). The organic layer was washed with brine (3x15 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by
 20 purified by silica gel chromatography to afford (*S*)-*tert*-butyl (1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (160 mg, 0.298 mmol, 50% yield) as a pale purple oil. LCMS (ESI) m/e 537.4 $[(M+H)^+]$, calcd $C_{28}H_{33}ClF_3N_2O_3$, 537.2]; LC/MS retention time (method A): t_R = 2.60 min; ^1H NMR (400MHz, CHLOROFORM-*d*) δ 8.95 (d, J =4.3 Hz, 1H), 8.19 (d, J =2.3 Hz, 1H), 7.81 (d, J =9.0 Hz, 1H), 7.71 (d, J =2.0 Hz, 1H), 7.62 (dd, J =8.5, 2.0 Hz, 1H), 7.50 (dd, J =8.9, 2.1 Hz, 1H), 7.33 (d, J =4.5 Hz, 1H), 7.20 (d, J =8.5 Hz, 1H), 4.39 - 4.17 (m, 2H), 2.00 - 1.79 (m, 3H), 1.44 (s, 3H), 1.42 (s, 9H), 1.03 (d, J =6.5 Hz, 3H), 1.01 (d, J =6.5 Hz, 3H).
 25

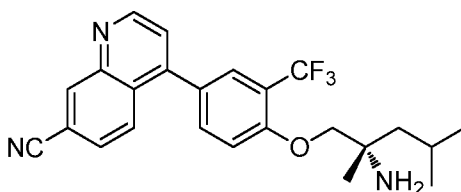


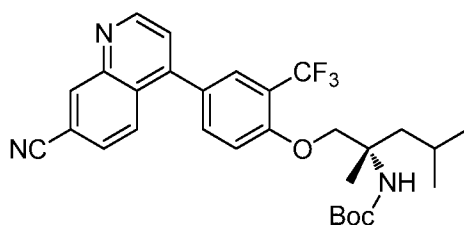
Part D: *(S)*-1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

(S)-*tert*-Butyl (1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (40 mg, 0.074 mmol) was treated with TFA (1 mL, 12.98 mmol) and stirred at ambient temperature for 30 min. The resultant was concentrated under reduced pressure. The residue was purified via preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5- μ m; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 45-85% B over 15 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.). Obtained *(S)*-1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine carbamate (160 mg, 0.298 mmol, 50% yield) as a colorless solid. LCMS (ESI) m/e 437.2 [(M+H)⁺, calcd C₂₃H₂₅ClF₃N₂O, 437.2]; LC/MS retention time (method D): t_R = 0.97 min; ¹H NMR (500MHz, DMSO-*d*₆) δ 8.98 (d, J =4.4 Hz, 1H), 8.17 (d, J =1.8 Hz, 1H), 7.88 (d, J =9.2 Hz, 1H), 7.83 (d, J =8.8 Hz, 1H), 7.78 (s, 1H), 7.66 (dd, J =9.2, 1.8 Hz, 1H), 7.55 (d, J =4.4 Hz, 1H), 7.44 (d, J =8.4 Hz, 1H), 3.96 - 3.83 (m, 2H), 1.86 - 1.77 (m, 1H), 1.41 (d, J =5.5 Hz, 2H), 1.14 (s, 3H), 0.94 (d, J =6.6 Hz, 3H), 0.93 (d, J =6.6 Hz, 3H).

Example 89

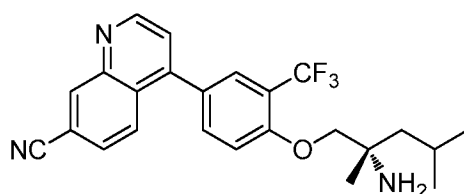
(S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)quinoline-7-carbonitrile





Part A: (*S*)-*tert*-butyl (1-(4-(7-cyanoquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

(*S*)-*tert*-butyl (1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (84 mg, 0.156 mmol) (prepared as described in Example 88), zinc cyanide (20.20 mg, 0.172 mmol), 1,1'-bis(diphenylphosphino)ferrocene (13.01 mg, 0.023 mmol), Pd₂(dba)₃ (7.16 mg, 7.82 μmol), *N,N*-dimethylformamide (1 mL), and water (0.10 mL) were charged to a pressure rated vial and the mixture was sparged with nitrogen for 5 minutes. The vial was sealed, purged of oxygen, and heated under nitrogen at 115 °C overnight. The resultant mixture was cooled to ambient temperature, vacuum filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10-80 % ethyl acetate/hexanes gradient elution) to afford (*S*)-*tert*-butyl (1-(4-(7-cyanoquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (22.5 mg, 0.043 mmol, 27% yield) as a near colorless film. LCMS (ESI) *m/e* 528.2 [(M+H)⁺, calcd C₂₉H₃₃F₃N₃O₃, 528.3]; LC/MS retention time (method D): *t*_R = 1.30 min.



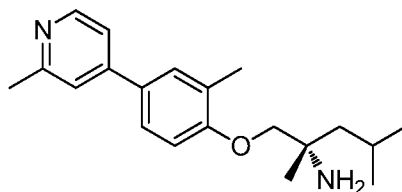
Part B: (*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)quinoline-7-carbonitrile

(*S*)-*tert*-Butyl (1-(4-(7-cyanoquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (22 mg, 0.042 mmol) was treated with TFA (964 μL, 12.51 mmol) and stirred at room temperature for 30 minutes. The resultant was concentrated under reduced pressure. The residue was purified via preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5-μm; Mobile Phase A: 5:95

acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5
 acetonitrile: water with 10-mM ammonium acetate; Gradient: 45-85% B over 15
 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.). Obtained (*S*)-4-(4-((2-
 amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)quinoline-7-carbonitrile
 5 (13.3 mg, 0.031 mmol, 75% yield) as a colorless solid. LCMS (ESI) m/e 428.2
 [(M+H)⁺, calcd C₂₄H₂₅F₃N₃O, 428.2]; LC/MS retention time (method D): t_R = 0.97
 min; ¹H NMR (500MHz, DMSO-d₆) δ 9.11 (d, J =4.4 Hz, 1H), 8.68 (s, 1H), 8.06 -
 7.98 (m, 1H), 7.92 (d, J =8.8 Hz, 1H), 7.84 (d, J =8.8 Hz, 1H), 7.81 (s, 1H), 7.70 (d,
 J =4.4 Hz, 1H), 7.45 (d, J =8.8 Hz, 1H), 4.00 - 3.77 (m, 2H), 1.82 (dt, J =12.7, 6.3 Hz,
 10 1H), 1.41 (d, J =5.5 Hz, 2H), 1.14 (s, 3H), 0.94 (d, J =6.5 Hz, 3H), 0.93 (d, J =6.5 Hz,
 3H).

Example 90

(*S*)-2,4-dimethyl-1-(2-methyl-4-(2-methylpyridin-4-yl)phenoxy)pentan-2-amine



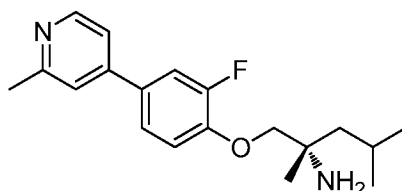
15

Prepared as described in Example 32 to afford (*S*)-2,4-dimethyl-1-(2-methyl-
 4-(2-methylpyridin-4-yl)phenoxy)pentan-2-amine carbonitrile (17 mg, 0.054 mmol,
 98% yield for the final step) as a colorless solid. LCMS (ESI) m/e 313.1 [(M+H)⁺,
 calcd C₂₀H₂₉N₂O, 313.2]; LC/MS retention time (method D): t_R = 0.65 min; ¹H NMR
 20 (500MHz, DMSO-d₆) δ 8.44 (d, J =5.1 Hz, 1H), 7.67 - 7.60 (m, 2H), 7.54 (s, 1H),
 7.45 (d, J =5.1 Hz, 1H), 7.05 (d, J =8.1 Hz, 1H),), 3.88 - 3.29 (m, 2H), 2.30 (s, 3H),
 1.91 (s, 3H), 1.81 (dt, J =12.8, 6.4 Hz, 1H), 1.64 - 1.55 (m, 1H), 1.53 - 1.44 (m, 1H),
 1.26 (s, 3H), 0.95 (d, J =6.6 Hz, 3H), 0.92 (d, J =6.6 Hz, 3H).

25

Example 91

(*S*)-1-(2-fluoro-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

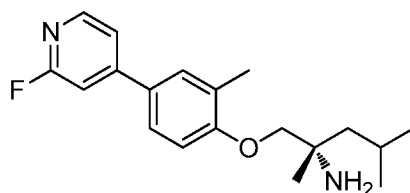


Prepared as described in Example 32 to afford (*S*)-1-(2-fluoro-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (12 mg, 0.037 mmol, 96% yield for the final step) as a colorless solid. LCMS (ESI) m/e 317.1 [(M+H)⁺, calcd C₁₉H₂₆FN₂O, 317.2]; LC/MS retention time (method D): t_R = 0.62 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.57 (d, J =5.5 Hz, 1H), 8.13 (br. s., 2H), 7.87 (d, J =12.5 Hz, 1H), 7.80 (s, 1H), 7.74 (d, J =9.2 Hz, 1H), 7.70 (d, J =5.1 Hz, 1H), 7.42 (t, J =8.6 Hz, 1H), 4.23 - 4.08 (m, 2H), 2.58 (s, 3H), 1.82 (dt, J =12.7, 6.1 Hz, 1H), 1.77 - 1.69 (m, 1H), 1.60 (dd, J =14.3, 5.1 Hz, 1H), 1.38 (s, 3H), 0.97 (d, J =6.6 Hz, 3H), 0.93 (d, J =6.2 Hz, 3H).

10

Example 92

(*S*)-1-(4-(2-fluoropyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine

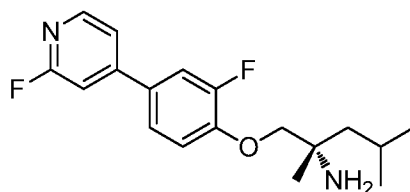


Prepared as described in Example 32 to afford (*S*)-1-(4-(2-fluoropyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine (4.8 mg, 0.015 mmol, 90% yield for the final step) as a colorless solid. LCMS (ESI) m/e 317.1 [(M+H)⁺, calcd C₁₉H₂₆FN₂O, 317.2]; LC/MS retention time (method D): t_R = 0.96 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.24 (d, J =5.1 Hz, 1H), 7.80 - 7.69 (m, 2H), 7.66 (d, J =5.1 Hz, 1H), 7.47 (s, 1H), 7.03 (d, J =8.1 Hz, 1H), 3.80 - 3.38 (m, 2H), 2.28 (s, 3H), 1.86 - 1.77 (m, 1H), 1.49 - 1.35 (m, 2H), 1.15 (s, 3H), 0.93 (t, J =6.2 Hz, 6H).

20

Example 93

(*S*)-1-(2-fluoro-4-(2-fluoropyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



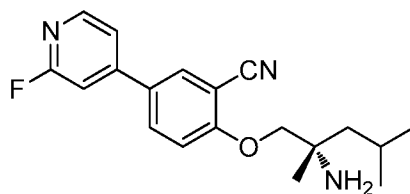
25

Prepared as described in Example 32 to afford (*S*)-1-(2-fluoro-4-(2-fluoropyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (10.8 mg, 0.034 mmol,

75% yield for the final step) as a colorless solid. LCMS (ESI) m/e 321.1 [(M+H)⁺, calcd C₁₈H₂₃F₂N₂O, 321.2]; LC/MS retention time (method D): t_R = 0.90 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.27 (d, J =5.1 Hz, 1H), 7.86 (dd, J =12.7, 2.0 Hz, 1H), 7.72 (d, J =5.9 Hz, 2H), 7.55 (s, 1H), 7.30 (t, J =8.8 Hz, 1H), 3.88 - 3.75 (m, 2H), 1.81 (dquin, J =12.7, 6.3 Hz, 1H), 1.48 - 1.31 (m, 2H), 1.13 (s, 3H), 0.93 (t, J =7.2 Hz, 6H).

Example 94

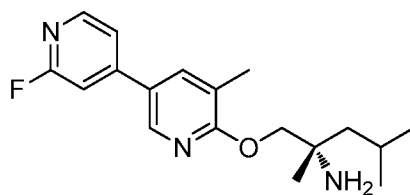
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-fluoropyridin-4-yl)benzonitrile



Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-fluoropyridin-4-yl)benzonitrile (16.9 mg, 0.051 mmol, 80% yield for the final step) as a colorless solid. LCMS (ESI) m/e 328.1 [(M+H)⁺, calcd C₁₉H₂₃FN₃O, 328.2]; LC/MS retention time (method D): t_R = 0.94 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.37 (d, J =2.2 Hz, 1H), 8.31 (d, J =5.1 Hz, 1H), 8.22 (dd, J =8.8, 2.2 Hz, 1H), 7.78 (d, J =5.1 Hz, 1H), 7.63 (s, 1H), 7.43 (d, J =9.2 Hz, 1H), 4.12 - 3.99 (m, 2H), 1.83 (dt, J =12.7, 6.3 Hz, 1H), 1.60 - 1.43 (m, 2H), 1.24 (s, 3H), 0.95 (t, J =6.4 Hz, 6H).

Example 95

(*S*)-1-((2'-fluoro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine

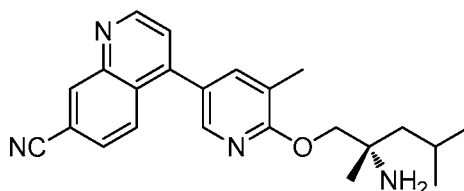


Prepared as described in Example 32 to afford (*S*)-1-((2'-fluoro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (6.5 mg, 0.020 mmol, 57% yield for the final step) as a colorless solid. LCMS (ESI) m/e 318.1 [(M+H)⁺, calcd C₁₈H₂₅FN₃O, 318.2]; LC/MS retention time (method D): t_R = 0.95 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.54 (d, J =2.2 Hz, 1H), 8.29 (d, J =5.1 Hz, 1H), 8.12 (s, 1H),

7.73 (d, $J=5.1$ Hz, 1H), 7.57 (s, 1H), 4.22 - 4.08 (m, 2H), 1.91 (s, 3H), 1.81 (dq, $J=12.7, 6.2$ Hz, 1H), 1.55 - 1.39 (m, 2H), 1.20 (s, 3H), 0.93 (dd, $J=8.8, 6.6$ Hz, 6H).

Example 96

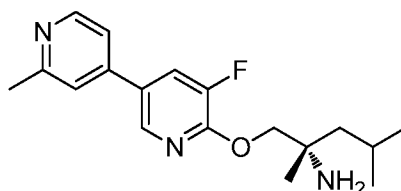
5 (S)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)quinoline-7-carbonitrile



Prepared as described in Example 89 to afford (S)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)quinoline-7-carbonitrile (9.9 mg, 0.026
10 mmol, 35% yield for the final step) as a colorless solid. LCMS (ESI) m/e 375.1 [(M+H)⁺, calcd C₂₃H₂₇N₄O, 375.2]; LC/MS retention time (method D): t_R = 0.94 min; ¹H NMR (600MHz, DMSO-d₆) δ 9.10 (d, $J=4.4$ Hz, 1H), 8.68 (s, 1H), 8.18 (s, 1H), 8.07 (d, $J=8.8$ Hz, 1H), 7.92 (d, $J=8.4$ Hz, 1H), 7.82 (br. s., 1H), 7.68 (d, $J=4.0$ Hz, 1H), 4.17 - 4.05 (m, 2H), 2.29 (s, 3H), 1.90 - 1.79 (m, 1H), 1.49 - 1.37 (m, 2H),
15 1.16 (s, 3H), 0.95 (t, $J=6.2$ Hz, 6H).

Example 97

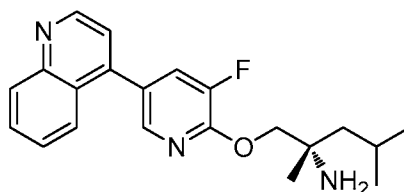
(S)-1-((5-fluoro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



20 Prepared as described in Example 32 to afford (S)-1-((5-fluoro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (4.8 mg, 0.015 mmol, 90% yield for the final step) as a colorless solid. LCMS (ESI) m/e 318.2 [(M+H)⁺, calcd C₁₈H₂₅FN₃O, 318.2]; LC/MS retention time (method D): t_R = 0.60 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.51 (d, $J=5.1$ Hz, 1H), 8.48 (s, 1H), 8.23 (d, $J=11.4$ Hz,
25 1H), 7.66 (s, 1H), 7.57 (d, $J=5.1$ Hz, 1H), 4.32 - 4.21 (m, 2H), 1.91 (s, 3H), 1.87 - 1.77 (m, 1H), 1.57 - 1.41 (m, 2H), 1.22 (s, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H).

Example 98

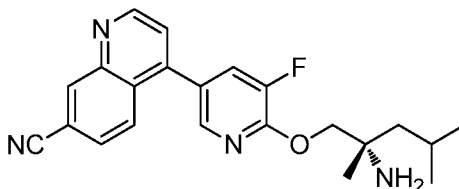
(*S*)-1-((3-fluoro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 32 to afford (*S*)-1-((3-fluoro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (8.4 mg, 0.024 mmol, 59% yield for the final step) as a colorless solid. LCMS (ESI) m/e 354.1 [(M+H)⁺, calcd C₂₁H₂₅FN₃O, 354.2]; LC/MS retention time (method D): t_R = 0.74 min; ¹H NMR (500MHz, DMSO-*d*₆) δ 8.98 (d, J =4.0 Hz, 1H), 8.18 (d, J =1.8 Hz, 1H), 8.14 (d, J =8.4 Hz, 1H), 8.03 (d, J =11.0 Hz, 1H), 7.91 (d, J =8.4 Hz, 1H), 7.84 (t, J =7.5 Hz, 1H), 7.70 - 7.62 (m, 1H), 7.54 (d, J =4.4 Hz, 1H), 4.27 - 4.17 (m, 2H), 1.85 (dt, J =12.7, 6.1 Hz, 1H), 1.53 - 1.38 (m, 2H), 1.19 (s, 3H), 0.96 (t, J =7.0 Hz, 6H).

Example 99

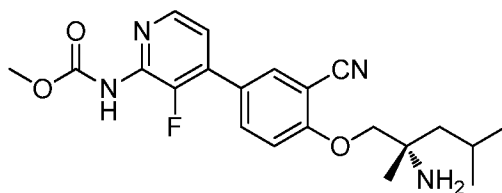
(*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)quinoline-7-carbonitrile



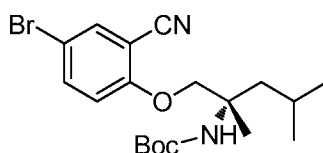
Prepared as described in Example 88 to (*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)quinoline-7-carbonitrile (5.6 mg, 0.014 mmol, 62% yield for the final step) as a colorless solid. LCMS (ESI) m/e 379.1 [(M+H)⁺, calcd C₂₂H₂₄FN₄O, 379.2]; LC/MS retention time (method D): t_R = 0.91 min; ¹H NMR (500MHz, DMSO-*d*₆) δ 9.13 (d, J =4.4 Hz, 1H), 8.70 (s, 1H), 8.19 (d, J =1.8 Hz, 1H), 8.09 (d, J =8.8 Hz, 1H), 8.06 - 8.01 (m, 1H), 7.98 - 7.90 (m, 1H), 7.73 (d, J =4.4 Hz, 1H), 4.22 - 4.10 (m, 2H), 1.85 (dt, J =12.7, 6.3 Hz, 1H), 1.50 - 1.35 (m, 2H), 1.15 (s, 3H), 0.95 (t, J =6.6 Hz, 6H).

Example 100

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate



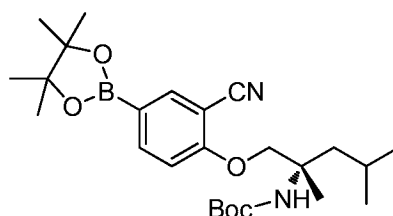
5



Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as in Example 32 Parts A-F to yield (*S*)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate. LC/MS retention time (method D): $t_R = 1.29$ min.

10



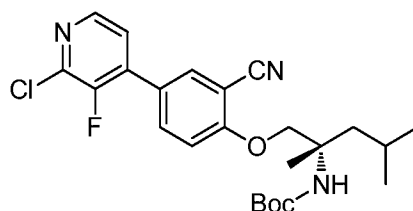
Part B: (S)-tert-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

15

(*S*)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.57 g, 1.386 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.422 g, 1.663 mmol), $\text{PdCl}_2(\text{dppf})$ (0.051 g, 0.069 mmol), potassium acetate (0.408 g, 4.16 mmol), and dioxane (5 mL) were charged to a pressure rated vial. The vial was purged of oxygen and the mixture stirred under nitrogen at 80 °C overnight. The mixture was cooled to ambient temperature, vacuum filtered, and concentrated under reduced pressure. Obtained (*S*)-tert-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (600 mg, 1.30 mmol, 100% crude yield) as a brown

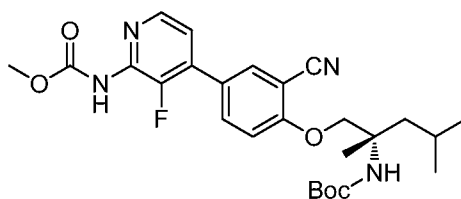
20

oil that was used without further purification. LCMS (ESI) m/e 481.1 $[(M+Na)^+]$, calcd $C_{25}H_{39}BN_2NaO_5$, 481.3]; LC/MS retention time (method B): t_R = 2.49 min.



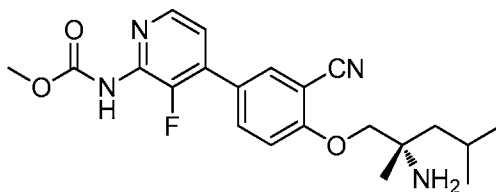
5 *Part C: (S)-tert-butyl (1-(4-(2-chloro-3-fluoropyridin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate*

A mixture of 2-chloro-3-fluoro-4-iodopyridine (105 mg, 0.408 mmol), (*S*)-*tert*-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (374 mg, 0.816 mmol), potassium carbonate (169
10 mg, 1.224 mmol), and $Pd(Ph_3P)_4$ (14.14 mg, 0.012 mmol) in toluene (1 mL), water (0.050 mL), and ethanol (0.100 mL) in a pressure rated 1 dram vial was purged of oxygen, and stirred under nitrogen at 80 °C overnight. The mixture was filtered via syringe tip filter and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10-80 % ethyl acetate/hexanes gradient elution) to
15 afford (*S*)-*tert*-butyl (1-(4-(2-chloro-3-fluoropyridin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (49 mg, 0.106 mmol, 26% yield) as a light yellow film. LCMS (ESI) m/e 462.0 $(M+H)^+$, calcd $C_{23}H_{30}ClFN_3O_3$, 462.2]; LC/MS retention time (method D): t_R = 1.30 min; ^1H NMR (400MHz, CHLOROFORM- d) δ 8.28 (d, J =5.0 Hz, 1H), 7.82 (dd, J =2.0, 1.0 Hz, 1H), 7.77 (dt, J =8.8, 1.9 Hz, 1H),
20 7.33 - 7.29 (m, 1H), 7.18 (d, J =9.0 Hz, 1H), 4.59 (s, 1H), 4.45 (d, J =8.8 Hz, 1H), 4.22 (d, J =9.0 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.91 - 1.79 (m, 1H), 1.56 - 1.50 (m, 1H), 1.46 (s, 3H), 1.40 (s, 9H), 1.03 (d, J =6.8 Hz, 6H).



Part D: (S)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate

A solution of (*S*)-*tert*-butyl (1-(4-(2-amino-3-fluoropyridin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (40 mg, 0.090 mmol) cooled to 0 °C was added methyl chloroformate (0.035 mL, 0.452 mmol) and pyridine (0.073 mL, 0.904 mmol) followed by DMAP (1.104 mg, 9.04 μmol). The cooling bath was removed and the mixture stirred overnight. The reaction mixture was concentrated under reduced pressure. Obtained (*S*)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate (20 mg, 0.040 mmol, 44% crude yield) which was used without further purification. LCMS (ESI) m/e 501.1 (M+H)⁺, calcd C₂₃H₃₀ClFN₃O₃, 501.3]; LC/MS retention time (method D): t_R = 1.17 min.

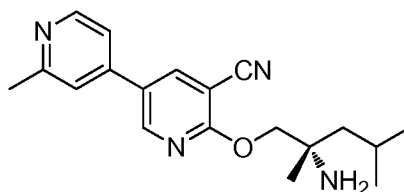


Part E: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate

(*S*)-Methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate (20 mg, 0.040 mmol) and TFA (1 mL, 12.98 mmol) were stored at ambient temperature for 2 hours. The resultant was concentrated under reduced pressure. The residue was purified via preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5-μm; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 45-85% B over 15 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min.). Obtained (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate (4.1 mg, 10.14 μmol, 25% yield for two steps) as a colorless solid. LCMS (ESI) m/e 401.0 (M+H)⁺, calcd C₂₁H₂₆FN₄O₃, 401.2]; LC/MS retention time (method D): t_R = 0.82 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.26 (d, J =4.8 Hz, 1H), 8.05 (s, 1H), 7.95 (d, J =9.5 Hz, 1H), 7.50 (t, J =5.1 Hz, 1H), 7.43 (d, J =8.8 Hz, 1H), 4.13 - 3.99 (m, 2H), 1.91 (s, 3H), 1.86 - 1.78 (m, 1H), 1.60 - 1.44 (m, 2H), 1.24 (s, 3H), 0.94 (t, J =5.9 Hz, 6H).

Example 101

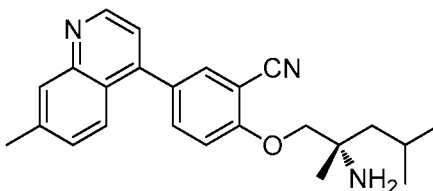
(*S*)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile



Prepared as described in Example 32 to afford (*S*)-6-((2-amino-2,4-
 5 dimethylpentyl)oxy)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile (16 mg, 0.054 mmol,
 44% yield for the final step) as a pale yellow oil. LCMS (ESI) m/e 325.1 [(M+H)⁺,
 calcd C₁₉H₂₅N₄O, 325.2]; LC/MS retention time (method D): t_R = 0.58 min; ¹H NMR
 (500MHz, DMSO-d₆) δ 9.02 (d, J =2.2 Hz, 1H), 8.92 (d, J =2.6 Hz, 1H), 8.68 (d,
 J =5.5 Hz, 1H), 8.42 (br. s., 2H), 7.99 (s, 1H), 7.89 (d, J =4.8 Hz, 1H), 4.74 - 4.47 (m,
 10 2H), 2.64 (s, 3H), 1.89 (dt, J =12.6, 6.4 Hz, 1H), 1.83 - 1.74 (m, 1H), 1.65 (dd,
 J =14.3, 5.5 Hz, 1H), 1.43 (s, 3H), 0.98 (d, J =1.8 Hz, 3H), 0.96 (d, J =1.8 Hz, 3H).

Example 102

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(7-methylquinolin-4-yl)benzonitrile

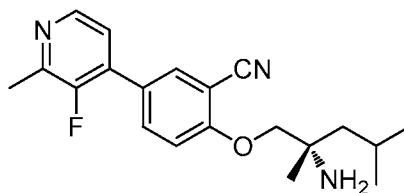


Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-
 15 dimethylpentyl)oxy)-5-(7-methylquinolin-4-yl)benzonitrile (76 mg, 0.195 mmol,
 53% yield for the final step) as a colorless film. LCMS (ESI) m/e 374.0 [(M+H)⁺,
 calcd C₂₄H₂₈N₃O, 374.2]; LC/MS retention time (method D): t_R = 0.76 min; ¹H NMR
 (600MHz, DMSO-d₆) δ 8.90 (d, J =4.0 Hz, 1H), 7.98 (s, 1H), 7.91 (s, 1H), 7.87 (dd,
 J =8.8, 2.2 Hz, 1H), 7.73 (d, J =8.4 Hz, 1H), 7.48 (dd, J =8.1, 4.8 Hz, 2H), 7.42 (d,
 J =4.0 Hz, 1H), 4.29 - 4.09 (m, 2H), 2.55 (s, 3H), 1.86 (dt, J =12.3, 6.3 Hz, 1H), 1.72
 20 (dd, J =13.9, 5.1 Hz, 1H), 1.58 (dd, J =14.1, 5.7 Hz, 1H), 1.35 (s, 3H), 0.97 (t, J =6.2
 Hz, 6H).

25

Example 103

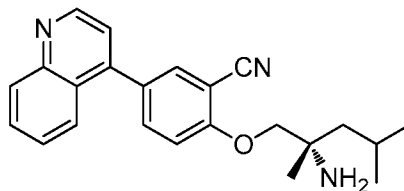
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(3-fluoro-2-methylpyridin-4-yl)benzonitrile



5 Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(3-fluoro-2-methylpyridin-4-yl)benzonitrile (7.7 mg, 0.022 mmol, 74% yield for the final step) as a colorless film. LCMS (ESI) m/e 342.0 [(M+H)⁺, calcd C₂₀H₂₅FN₃O, 342.2]; LC/MS retention time (method D): t_R = 0.79 min; ¹H NMR (600MHz, DMSO-d₆) δ 8.35 (d, J =4.8 Hz, 1H), 8.05 (s, 1H), 7.95 (d, J =8.8 Hz, 1H), 7.48 (br. s., 1H), 7.39 (d, J =8.8 Hz, 1H), 3.96 - 3.83 (m, 2H), 2.51 (s, 3H), 1.82 (dt, J =12.1, 6.1 Hz, 1H), 1.52 - 1.37 (m, 2H), 1.15 (s, 3H), 0.93 (t, J =5.0 Hz, 6H).

Example 104

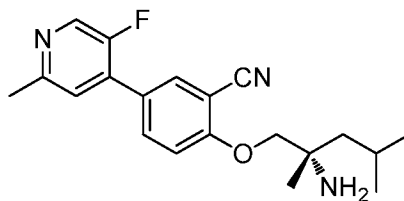
15 (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(quinolin-4-yl)benzonitrile



Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(quinolin-4-yl)benzonitrile (23 mg, 0.061 mmol, 14% yield for the final step) as a colorless film. LCMS (ESI) m/e 360.0 [(M+H)⁺, calcd C₂₃H₂₆N₃O, 360.2]; LC/MS retention time (method D): t_R = 0.69 min; ¹H NMR (600MHz, DMSO-d₆) δ 8.97 (d, J =4.4 Hz, 1H), 8.13 (d, J =8.4 Hz, 1H), 7.99 (s, 1H), 7.90 - 7.79 (m, 3H), 7.64 (t, J =7.2 Hz, 1H), 7.50 (d, J =4.4 Hz, 1H), 7.47 (d, J =8.8 Hz, 1H), 4.11 - 3.98 (m, 2H), 1.86 (dquin, J =12.5, 6.4 Hz, 1H), 1.63 - 1.45 (m, 2H), 1.25 (s, 3H), 0.97 (t, J =6.2 Hz, 6H).

Example 105

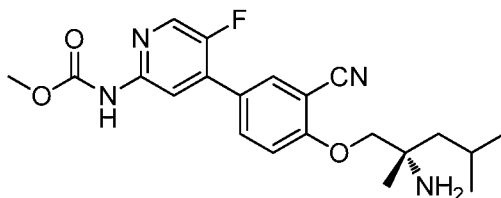
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5-fluoro-2-methylpyridin-4-yl)benzonitrile



5 Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5-fluoro-2-methylpyridin-4-yl)benzonitrile (9.5 mg, 0.026 mmol, 25% yield for the final step) as a pale yellow film. LCMS (ESI) m/e 342.0 [(M+H)⁺, calcd C₂₀H₂₅FN₃O, 342.2]; LC/MS retention time (method D): t_R = 0.80 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.50 (d, J =2.6 Hz, 1H), 8.08 (d, J =1.8 Hz, 1H), 7.97 (d, J =8.1 Hz, 1H), 7.56 (d, J =6.6 Hz, 1H), 7.40 (d, J =8.8 Hz, 1H), 3.96 - 3.85 (m, 2H), 2.52 (s, 3H), 1.86 - 1.77 (m, 1H), 1.51 - 1.36 (m, 2H), 1.15 (s, 3H), 10 0.94 (d, J =3.7 Hz, 3H), 0.93 (d, J =3.7 Hz, 3H).

Example 106

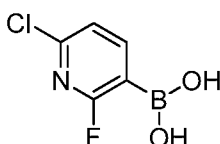
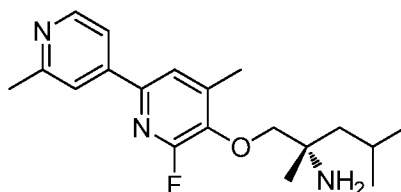
15 (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-5-fluoropyridin-2-yl)carbamate



Prepared as described in Example 100 to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-5-fluoropyridin-2-yl)carbamate (20.5 mg, 0.050 mmol, 36% yield for the final step) as a colorless film. LCMS (ESI) m/e 401.0 (M+H)⁺, calcd C₂₁H₂₆FN₄O₃, 401.2]; LC/MS retention time (method D): t_R = 0.91 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.38 (s, 1H), 8.02 (s, 1H), 7.97 (d, J =5.9 Hz, 1H), 7.91 (d, J =9.2 Hz, 1H), 7.41 (d, J =8.8 Hz, 1H), 3.96 - 3.84 (m, 2H), 2.52 (s, 3H), 1.82 (dt, J =12.7, 6.3 Hz, 1H), 1.49 - 1.34 (m, 2H), 1.15 (s, 3H), 0.94 (d, J =3.7 Hz, 3H), 0.93 (d, J =3.7 Hz, 3H). 25

Example 107

(*S*)-1-((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

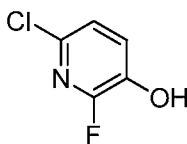


5

Part A: (6-chloro-2-fluoropyridin-3-yl)boronic acid

A solution of LDA (1M in THF) (8.36 ml, 8.36 mmol) at -78 °C was treated dropwise with a solution of 2-chloro-6-fluoropyridine (1.0 g, 7.60 mmol) in THF (2 mL). The mixture was maintained at -78 °C for 1 h and then treated with a solution of triisopropyl borate (1.765 ml, 7.60 mmol) in THF (1 mL). The reaction mixture was treated with water (4 mL) and concentrated under reduced pressure to afford (6-chloro-2-fluoropyridin-3-yl)boronic acid (1.33 g, 7.60 mmol, 100% crude yield) as a pale orange waxy solid that was used without further purification. LCMS (ESI) m/e 176.0 ($M+H$)⁺, calcd C₅H₅BClFNO₂, 176.0]; LC/MS retention time (method D): t_R = 0.71 min.

15

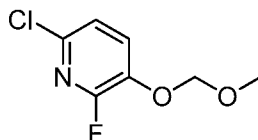


Part B: 6-chloro-2-fluoropyridin-3-ol

A suspension of (6-chloro-2-fluoropyridin-3-yl)boronic acid (1.3 g, 7.41 mmol) in NaOH (4.45 ml, 22.24 mmol) at 0 °C was treated all at once with hydrogen peroxide (0.500 ml, 8.15 mmol). The mixture was stirred at ambient temperature overnight. The resulting solution was quenched with ice water, acidified with 3 N aqueous hydrochloric acid to pH = 5, and extracted three times with ethyl acetate. The pooled organics were dried over sodium sulfate and concentrated under reduced pressure to afford 6-chloro-2-fluoropyridin-3-ol (1.08 g, 7.32 mmol, 99% crude yield) as a waxy solid that was used without further purification. LCMS (ESI) m/e

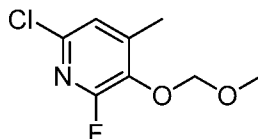
20
25

148.0 (M+H)⁺, calcd C₅H₄ClFNO, 148.0]; LC/MS retention time (method D): *t*_R = 0.83 min.



5 *Part C: 6-chloro-2-fluoro-3-(methoxymethoxy)pyridine*

A solution of 6-chloro-2-fluoropyridin-3-ol (0.49 g, 3.32 mmol), MOM-Cl (0.277 mL, 3.65 mmol), potassium carbonate (0.551 g, 3.99 mmol) in acetone (20 mL) was stirred at 60 °C for 3 h. The mixture was cooled to ambient temperature and vacuum filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5-30 % ethyl acetate/hexanes) to afford 6-chloro-2-fluoro-3-(methoxymethoxy)pyridine (0.24 g, 1.25 mmol, 38% yield for three steps) as a near colorless oil. LCMS (ESI) *m/e* 192.0 (M+H)⁺, calcd C₇H₈ClFNO₂, 192.0]; LC/MS retention time (method D): *t*_R = 1.20 min; ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.57 (dd, *J*=9.8, 8.3 Hz, 1H), 7.16 (d, *J*=8.3 Hz, 1H), 5.24 (s, 2H), 3.56 - 3.52 (m, 3H).

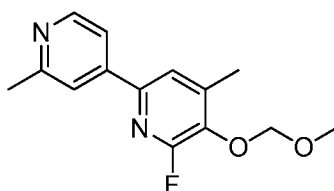


Part D: 6-chloro-2-fluoro-3-(methoxymethoxy)-4-methylpyridine

A solution of 6-chloro-2-fluoro-3-(methoxymethoxy)pyridine (0.24 g, 1.253 mmol) in tetrahydrofuran (9 mL) at -78 °C was treated dropwise with LDA (1.378 mL, 1.378 mmol). The resulting orange solution was maintained at -78 °C for 1 h and then treated dropwise with a solution of methyl iodide (0.094 mL, 1.503 mmol) in THF (0.5 mL). The resulting solution was stirred at -78 °C for 30 min. The resulting solution was warmed to ambient temperature, quenched with saturated aqueous ammonium chloride (5 mL), and stirred overnight. The layers were separated and the aqueous layer was extracted with ethyl acetate. The pooled organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5-30 % ethyl acetate/hexanes) afforded 6-chloro-2-fluoro-3-(methoxymethoxy)-4-methylpyridine

(0.22 g, 1.07 mmol, 85% yield) as a colorless oil. LCMS (ESI) m/e 206.1 (M+H)⁺, calcd C₈H₁₀ClFNO₂, 206.0]; LC/MS retention time (method D): t_R = 1.05 min; ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.07 (s, 1H), 5.21 - 5.10 (m, 2H), 3.64 - 3.54 (m, 3H), 2.37 (d, J =1.0 Hz, 3H).

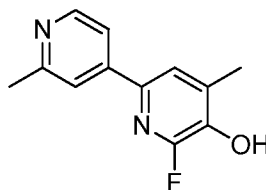
5



Part E: 6-fluoro-5-(methoxymethoxy)-2',4'-dimethyl-2,4'-bipyridine

To a pressure rated vial was added 6-chloro-2-fluoro-3-(methoxymethoxy)-4-methylpyridine (110 mg, 0.535 mmol), (2-methylpyridin-4-yl)boronic acid (81 mg, 0.588 mmol), cesium carbonate (349 mg, 1.070 mmol), toluene (1 mL), and ethanol (0.200 mL). The solution was sparged with a stream of nitrogen for 5 min. Tetrakis(triphenylphosphine)palladium(0) (43.3 mg, 0.037 mmol) was added and the vial was sealed, purged of oxygen, and stirred under nitrogen at 85 °C overnight. The resulting suspension was vacuum filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5-40 % ethyl acetate/hexanes gradient elution) to afford 6-fluoro-5-(methoxymethoxy)-2',4'-dimethyl-2,4'-bipyridine (40 mg, 0.153 mmol, 29 % yield) as a near colorless oil. LCMS (ESI) m/e 263.1 (M+H)⁺, calcd C₁₄H₁₆FN₂O₂, 263.1]; LC/MS retention time (method D): t_R = 0.80 min; ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.59 (d, J =5.3 Hz, 1H), 7.73 (s, 1H), 7.61 (dd, J =5.3, 1.3 Hz, 1H), 7.55 (s, 1H), 5.24 (d, J =1.0 Hz, 2H), 3.63 (s, 3H), 2.65 (s, 3H), 2.47 (s, 3H).

20

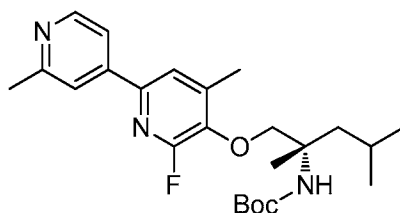


Part F: 6-fluoro-2',4'-dimethyl-[2,4'-bipyridin]-5-ol

A solution of 6-fluoro-5-(methoxymethoxy)-2',4'-dimethyl-2,4'-bipyridine (40 mg, 0.153 mmol) in methanol (5 mL) and HCl (conc.) (0.05 mL, 0.600 mmol) was stirred at 65 °C for 1 h and then concentrated under reduced pressure to afford 6-

25

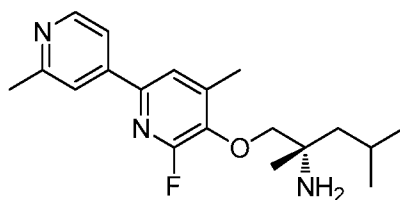
fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-ol (30 mg, 0.137 mmol, 90 % yield) as a pale tan solid. Used without further purification. LCMS (ESI) m/e 219.1 ($M+H$)⁺, calcd C₁₂H₁₂FN₂O, 219.1]; LC/MS retention time (method D): t_R = 0.59 min.



5

Part G: (S)-tert-butyl (1-(((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

A solution of 6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-ol (30 mg, 0.137 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (48.4 mg, 0.165 mmol), and cesium carbonate (134 mg, 0.412 mmol) in *N,N*-dimethylformamide (1 mL) in a pressure rated vial was stirred at 80 °C overnight. The mixture was cooled to ambient temperature and filtered through a syringe tip filter. Obtained (*S*)-*tert*-butyl (1-(((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (38.6 mg, 0.089 mmol, 65% crude yield) as a colorless oil that was used without further purification. LCMS (ESI) m/e 432.2 ($M+H$)⁺, calcd C₂₄H₃₅FN₃O₃, 432.3]; LC/MS retention time (method D): t_R = 1.08 min.



20 *Part H: (S)-1-(((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine*

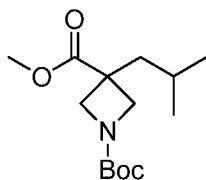
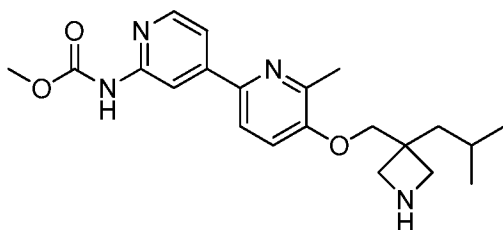
A solution of (*S*)-*tert*-butyl (1-(((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (38 mg, 0.088 mmol) in DMF (1 mL) was treated with TFA (1 mL, 12.98 mmol) and stirred at ambient temperature overnight. The solution was concentrated under reduced pressure. The crude material was purified via preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5-μm; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate;

Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 15 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min).

Obtained (*S*)-1-((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (20 mg, 0.060 mmol, 68% crude yield) as a colorless oil that was used without further purification. LCMS (ESI) m/e 332.3 ($M+H$)⁺, calcd C₁₉H₂₇FN₃O, 332.2]; LC/MS retention time (method D): t_R = 0.64 min; ¹H NMR (500MHz, DMSO-*d*₆) δ 8.54 (d, J =5.1 Hz, 1H), 7.99 (s, 1H), 7.83 (s, 1H), 7.74 (d, J =4.4 Hz, 1H), 3.84 – 3.80 (m, 2H), 2.55 (s, 3H), 2.41 (s, 3H), 1.88 - 1.75 (m, 1H), 1.49 - 1.31 (m, 2H), 1.15 (s, 3H), 1.00 - 0.90 (m, 6H).

Example 108

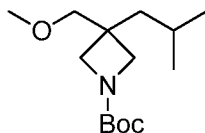
methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate



Part A: 1-*tert*-butyl 3-methyl 3-isobutylazetidine-1,3-dicarboxylate

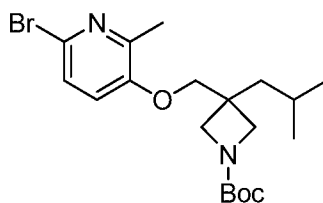
A solution of 1-*tert*-butyl 3-methyl azetidine-1,3-dicarboxylate (5.0 g, 23.23 mmol) and 1-iodo-2-methylpropane (21.37 g, 116 mmol) in tetrahydrofuran (100 mL) at -78 °C was treated dropwise with KHMDS (69.7 mL, 34.8 mmol). The solution was stirred at ambient temperature overnight. The resulting suspension was diluted with ethyl acetate (500 mL), washed with 0.5 N aqueous hydrochloric acid (2x100 mL), and brine (1x100 mL), dried over sodium sulfate and concentrated. The residue was purified via silica gel chromatography purification (2-20 % ethyl acetate/hexanes gradient elution) to afford 1-*tert*-butyl 3-methyl 3-isobutylazetidine-1,3-dicarboxylate (3.37 g, 12.42mmol, 54% yield) as an amber oil. ¹H NMR

(400MHz, CHLOROFORM-d) δ 4.22 (d, $J=8.8$ Hz, 2H), 3.82 - 3.70 (m, 5H), 1.87 (d, $J=7.0$ Hz, 2H), 1.63 - 1.51 (m, 1H), 1.45 (s, 9H), 0.89 (d, $J=6.8$ Hz, 6H).



5 *Part B: tert-butyl 3-isobutyl-3-(methoxymethyl)azetidine-1-carboxylate*

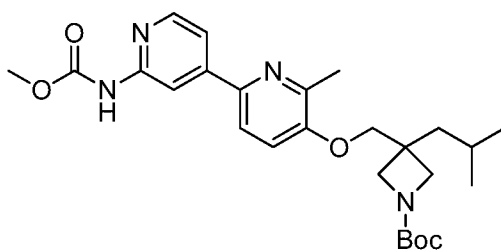
A solution of 1-*tert*-butyl 3-methyl 3-isobutylazetidine-1,3-dicarboxylate (2.51 g, 9.25 mmol) in tetrahydrofuran (40 mL) at ambient temperature was treated with lithium borohydride (0.403 g, 18.50 mmol) and stirred at 70 °C for 3 h. TLC indicated 50 % consumption of starting material. The reaction mixture was treated
 10 with additional lithium borohydride (0.302 g, 13.97 mmol) and stirred for 1.5 h at 70 °C. TLC indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C, quenched with 0.1N aqueous hydrochloric acid, and then diluted with ethyl acetate. The layers were separated and the aqueous extracted with ethyl acetate (2x). The pooled organics were dried over sodium sulfate, filtered, and
 15 concentrated under reduced pressure. The residue was purified by silica gel chromatography (10-80 % ethyl acetate/hexanes gradient elution) to afford *tert*-butyl 3-isobutyl-3-(methoxymethyl)azetidine-1-carboxylate (2.07 g, 8.51 mmol, 92% yield) as a colorless oil. ¹H NMR (400MHz, CHLOROFORM-d) δ 3.81 - 3.70 (m, 4H), 3.64 (d, $J=8.5$ Hz, 2H), 1.74 (tt, $J=13.5, 6.7$ Hz, 2H), 1.60 (d, $J=7.0$ Hz, 2H),
 20 1.46 (s, 9H), 0.91 (d, $J=6.5$ Hz, 6H).



Part C: tert-butyl 3-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-3-isobutylazetidine-1-carboxylate

25 A solution of *tert*-butyl 3-(hydroxymethyl)-3-isobutylazetidine-1-carboxylate (0.582 g, 2.392 mmol) in tetrahydrofuran (4 mL) was charged to a pressure rated vial and treated dropwise with KOtBu (1M in THF) (2.392 mL, 2.392 mmol). After 5 minutes, 6-bromo-3-fluoro-2-methylpyridine (0.50 g, 2.63 mmol) in THF (2 mL) was

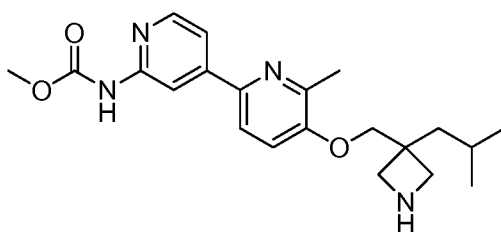
added all at once. The vial was sealed and heated to 80 °C overnight. The mixture was partitioned between ethyl acetate and brine. The layers were separated and the aqueous extracted with ethyl acetate (2x). The pooled organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified
 5 via silica gel chromatography to afford *tert*-butyl 3-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-3-isobutylazetidine-1-carboxylate (50 mg, 0.121 mmol, 5% yield) as a near colorless oil. LCMS (ESI) m/e 313.0 (M-Boc+H)⁺, calcd C₁₄H₂₂BrN₂O, 313.1]; LC/MS retention time (method D): t_R = 0.92 min.



10

Part D: tert-butyl 3-isobutyl-3-(((2'-((methoxycarbonyl)amino)-6-methyl-[2,4'-bipyridin]-5-yl)oxy)methyl)azetidine-1-carboxylate

A solution of (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (50 mg, 0.255 mmol), *tert*-butyl 3-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-3-isobutylazetidine-1-carboxylate (70.3 mg, 0.170 mmol), Pd(Ph₃P)₄ (13.76 mg, 0.012
 15 mmol), and cesium carbonate (111 mg, 0.340 mmol) in toluene (1 mL), and ethanol (0.1 mL) was charged to a pressure rated vial and sparged with a stream of nitrogen for 5 min. The vial was sealed, purged of oxygen, and stirred under nitrogen at 80 °C overnight. The mixture was cooled to ambient temperature and concentrated under
 20 reduced pressure. The residue was purified by silica gel chromatography (10-80 % ethyl acetate/hexanes gradient elution) to afford *tert*-butyl 3-isobutyl-3-(((2'-((methoxycarbonyl)amino)-6-methyl-[2,4'-bipyridin]-5-yl)oxy)methyl)azetidine-1-carboxylate (29 mg, 0.060 mmol, 35% yield) as a pale yellow film. LCMS (ESI) m/e 485.1 (M+H)⁺, calcd C₂₆H₃₇N₄O₅, 485.3]; LC/MS retention time (method D): t_R =
 25 1.14 min.

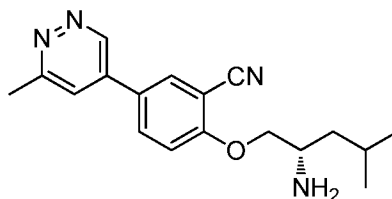


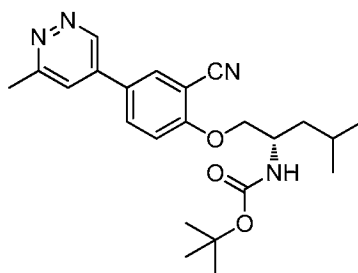
Part D: methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

Tert-butyl 3-isobutyl-3-(((2'-((methoxycarbonyl)amino)-6-methyl-[2,4'-bipyridin]-5-yl)oxy)methyl)azetidine-1-carboxylate (29 mg, 0.060 mmol) and TFA (1 mL, 12.98 mmol) were stirred at ambient temperature for 3 h. The solution was concentrated under reduced pressure. The crude material was purified via preparative HPLC (Column: XBridge C18, 19 x 200 mm, 5- μ m; Mobile Phase A: 5:95 methanol: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 methanol: water with 10-mM ammonium acetate; Gradient: 40-80% B over 40 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min). Obtained methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate (11.5 mg, 0.030 mmol, 50% yield) as a colorless film. LCMS (ESI) m/e 385.1 (M+H)⁺, calcd C₂₁H₂₉N₄O₃, 385.3]; LC/MS retention time (method D): t_R = 0.76 min; ¹H NMR (500MHz, DMSO-d₆) δ 8.49 (s, 1H), 8.31 (d, J =5.1 Hz, 1H), 7.86 (d, J =8.4 Hz, 1H), 7.64 (d, J =4.4 Hz, 1H), 7.56 (d, J =8.4 Hz, 1H), 4.27 (s, 2H), 3.54 - 3.38 (m, 4H), 2.46 (s, 3H), 1.86 (m, 3H), 1.73 - 1.59 (m, 3H), 0.86 (d, J =5.9 Hz, 6H).

Example 109

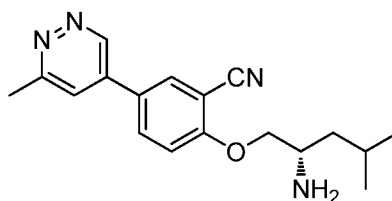
(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile





Part A: (S)-tert-butyl (1-(2-cyano-4-(6-methylpyridazin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate

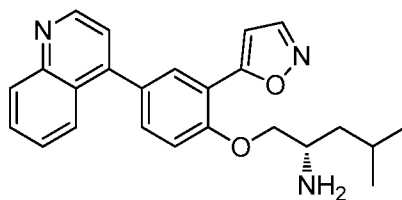
To a 2 mL vial was added (6-methylpyridazin-4-yl)boronic acid (20.56 mg, 0.149 mmol), (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-4-methylpentan-2-yl)carbamate (42.3 mg, 0.106 mmol), and Na₂CO₃ (0.160 mL, 0.319 mmol) in dioxane (0.5 mL) to give a colorless suspension under nitrogen. 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene (4.38 mg, 5.32 μmol) was added under nitrogen. The vial was sealed and heated at 100 °C (bath: 108 °C) for 2 h. The mixture was diluted with EtOAc, dried with Na₂SO₄, and passed through a plug of Na₂SO₄. The organic solution was concentrated to afford the desired product (70 mg, 100% crude yield) as a tan oil, which was directly used in the next step. LCMS (ESI) *m/e* 411.2 [(M+H)⁺, calcd C₂₃H₃₁N₄O₃, 411.2].



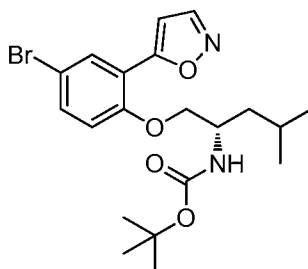
Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile

Prepared as previously described in Example 7, Part B to afford (S)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile (20.8 mg, 63% for 2 steps) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 9.51 (d, *J* = 2.4 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.24 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 4.11 (dd, *J* = 9.7, 5.1 Hz, 1H), 4.04 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.17 (t, *J* = 6.6 Hz, 1H), 2.67 (s, 3H), 1.84 (p, *J* = 6.6 Hz, 1H), 1.38 (ddd, *J* = 13.5, 8.3, 5.0 Hz, 1H), 1.30 (dq, *J* = 13.9, 7.0, 6.4 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 311.2 [(M+H)⁺, calcd C₁₈H₂₃N₄O, 311.2]; LC/MS retention time (method B): *t_R* = 1.46 min.

Example 110

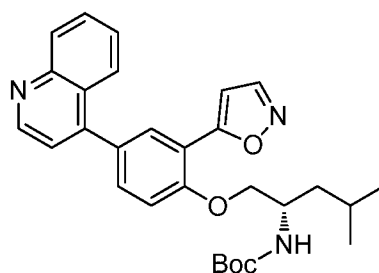
(S)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine

5



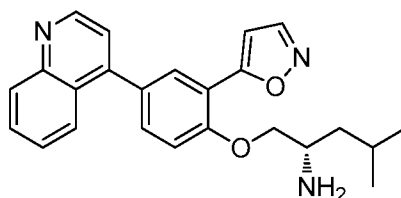
Part A: (S)-tert-butyl (1-(4-bromo-2-(isoxazol-5-yl)phenoxy)-4-methylpentan-2-yl)carbamate

To a 15 mL vial was added (*S*)-*tert*-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (204 mg, 0.939 mmol), Ph₃P (320 mg, 1.220 mmol), and 4-bromo-2-(isoxazol-5-yl)phenol (225 mg, 0.939 mmol) in tetrahydrofuran (3 mL) to give a tan solution. DIAD (0.256 mL, 1.314 mmol) was added at rt. The resultant clear tan solution was stirred at rt overnight for 18 h. The solution was concentrated to a dense oil and was directly purified by silica gel chromatography (up to 40% EtOAc/hexane) to afford (*S*)-*tert*-butyl (1-(4-bromo-2-(isoxazol-5-yl)phenoxy)-4-methylpentan-2-yl)carbamate (319 mg, 77%) as a white solid: ¹H NMR (400 MHz, Chloroform-d) δ 8.31 (s, 1H), 8.09 (d, *J* = 2.4 Hz, 1H), 7.46 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 2H), 4.60 (d, *J* = 8.9 Hz, 1H), 4.19 (d, *J* = 7.0 Hz, 1H), 4.02 (qd, *J* = 9.2, 5.2 Hz, 2H), 1.75 (dq, *J* = 13.6, 6.7 Hz, 1H), 1.46 (d, *J* = 12.0 Hz, 11H), 0.98 (d, *J* = 6.6 Hz, 6H).



Part B: (*S*)-tert-butyl (1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate

Prepared as previously described in Example 109 to afford (*S*)-tert-butyl (1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-yl)carbamate.
 LCMS (ESI) m/e 488.4 $[(M+H)^+]$, calcd $C_{29}H_{34}N_3O_4$, 488.2; LC/MS retention time (method A): t_R = 2.27 min.

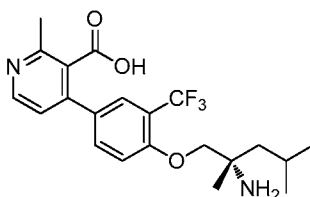


Part C: (*S*)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine

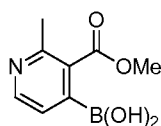
Prepared as previously described in Example 7, Part B to afford (*S*)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine (12.9 mg, 44% for two steps): ^1H NMR (500 MHz, DMSO- d_6) δ 8.97 (d, J = 4.4 Hz, 1H), 8.72 (d, J = 1.8 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 7.70 (dd, J = 8.5, 2.3 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.54 (d, J = 4.4 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.06 (d, J = 1.9 Hz, 1H), 4.13 (dd, J = 9.4, 4.9 Hz, 1H), 4.05 (dd, J = 9.4, 6.2 Hz, 1H), 3.25 (dq, J = 10.4, 5.6 Hz, 1H), 1.85 (dt, J = 13.4, 7.5 Hz, 1H), 1.41 (ddd, J = 13.4, 8.4, 4.7 Hz, 1H), 1.32 (ddd, J = 13.8, 8.7, 5.6 Hz, 1H), 0.93 (dd, J = 9.2, 6.6 Hz, 6H); LCMS (ESI) m/e 388.1 $[(M+H)^+]$, calcd $C_{24}H_{26}N_3O_2$, 388.2; LC/MS retention time (method B): t_R = 1.59 min.

Example 111

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-methylnicotinic acid

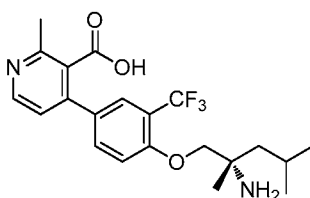


5



Part A: (3-(methoxycarbonyl)-2-methylpyridin-4-yl)boronic acid

To a vial was added methyl 4-chloro-2-methylnicotinate (52 mg, 0.280
 10 mmol), hypodiboric acid (37.7 mg, 0.420 mmol), 2-(dicyclohexylphosphino))-2',4',6'-
 triisopropylbiphenyl (2.67 mg, 5.60 μ mol), Xphos precatalyst (2.204 mg, 2.80 μ mol)
 and potassium acetate (82 mg, 0.840 mmol) in ethanol (2.6 mL) to give a tan
 suspension (degassed before adding reagents). The vial was capped and heated at 80
 °C for 1 h. LCMS showed conversion of the starting material to a new polar peak but
 15 with no parent ion. The mixture was directly used in the next step.



Part B: (S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-methylnicotinic acid

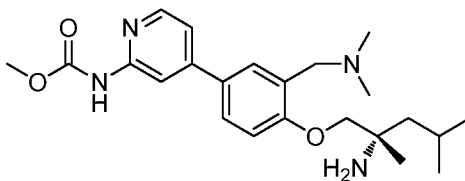
20 To a 20 mL vial was added (3-(methoxycarbonyl)-2-methylpyridin-4-
 yl)boronic acid (48.9 mg, 0.251 mmol) (previous reaction vessel) was added
 potassium phosphate tribasic (2.2 mL, 1.100 mmol). After degassing for 5 min,
 Xphos precatalyst (4.5 mg, 5.72 μ mol) and (*S*)-1-(4-bromo-2-
 (trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (33 mg, 0.084 mmol) and
 25 tetrahydrofuran (2.2 mL) were added. The vial was sealed and heated at 80 °C

overnight for 18 h. Volatiles were blown off. The residue was partitioned between EtOAc and water. The organic layer was dried, filtered and concentrated. The residue was dissolved in MeOH and purified by prep-HPLC to afford (*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-methylnicotinic acid
 5 (18.8 mg, 53%): ^1H NMR (600 MHz, DMSO- d_6) δ 8.27 (d, J = 5.1 Hz, 1H), 7.88 (s, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 5.2 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 3.99 - 3.92 (m, 2H), 2.47 (s, 3H), 1.88 - 1.72 (m, 1H), 1.60 - 1.45 (m, 2H), 1.24 (s, 3H), 0.89 (d, J = 6.5 Hz, 6H); LCMS (ESI) m/e 433.2 [(M+Na) $^+$, calcd $\text{C}_{21}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_3\text{Na}$, 433.2]; LC/MS retention time (method C): t_R = 2.60 min.

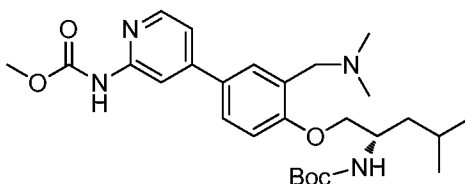
10

Example 112

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 ((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate

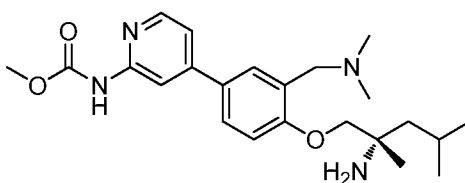


15



Part A: (*S*)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-
 ((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate

To a 2 mL vial was added crude aldehyde (prepared as described in Example
 20 32 (10.68 mg, 0.022 mmol) in CH_2Cl_2 (0.5 mL) to give a tan solution.
 Dimethylamine (0.110 mL, 0.220 mmol) (2.0 M in THF, excess) was added,
 followed by sodium triacetoxyborohydride (0.019 g, 0.088 mmol). The mixture was
 stirred at rt overnight for 16 h. LCMS showed complete conversion to the desired
 product ($M + H = 515.2$). The mixture was partitioned between water and EtOAc.
 25 The layers were separated. The organic layer was washed with brine, dried and
 concentrated. The tan residue was directly carried onto next reaction.

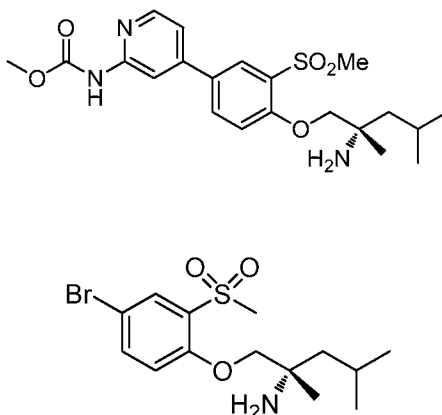


Part B: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate

Prepared as previously described in Example 7, Part B to afford (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate (5.5 mg, 60% for three steps): ¹H NMR (500 MHz, DMSO-d₆) δ 8.28 (d, *J* = 5.3 Hz, 1H), 8.10 (s, 1H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 3.83 (s, 2H), 3.70 (s, 3H), 3.51 (s, 2H), 2.20 (s, 6H), 1.81 (dt, *J* = 12.6, 6.4 Hz, 1H), 1.46 (qd, *J* = 14.0, 5.6 Hz, 2H), 1.19 (s, 3H), 0.94 (t, *J* = 6.1 Hz, 6H); LCMS (ESI) *m/e* 415.1 [(M+H)⁺, calcd C₂₃H₃₅N₄O₃, 415.3]; LC/MS retention time (method B): *t_R* = 1.43 min.

Example 113

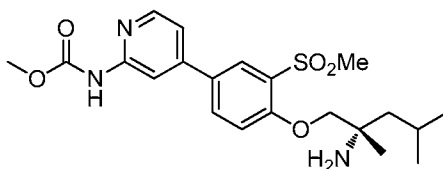
(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(methylsulfonyl)phenyl)pyridin-2-yl)carbamate



Part A: (S)-1-(4-bromo-2-(methylsulfonyl)phenoxy)-2,4-dimethylpentan-2-amine

To a 5 mL vial was added (S)-2-amino-2,4-dimethylpentan-1-ol (120 mg, 0.915 mmol) in tetrahydrofuran (1.2 mL) to give a colorless solution. Potassium *tert*-butoxide (1.097 mL, 1.097 mmol) (1.0 M in THF) was added dropwise under nitrogen. After 5 min, 4-bromo-1-fluoro-2-(methylsulfonyl)benzene (243 mg, 0.960 mmol) was added in one portion. The bottle was sealed and the mixture was stirred at 70 °C for 18 h. The mixture was partitioned between water and EtOAc. The

layers were separated. The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried and concentrated to a red oil (313 mg, 94%): ^1H NMR (400 MHz, Chloroform- d) δ 8.10 (d, J = 2.6 Hz, 1H), 7.69 (dd, J = 8.8, 2.5 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.90 (q, J = 8.5 Hz, 2H), 3.24 (s, 3H), 1.90
 5 - 1.75 (m, 1H), 1.52 (dd, J = 5.7, 3.5 Hz, 2H), 1.28 (s, 3H), 1.01 (dd, J = 10.6, 6.7 Hz, 6H); LCMS (ESI) m/e 363.9 [(M+H) $^+$, calcd C₁₄H₂₃BrNO₃S, 364.1]; LC/MS retention time (method B): t_R = 1.64 min.



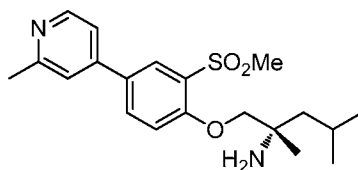
10 *Part B: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(methylsulfonyl)phenyl)pyridin-2-yl)carbamate*

Prepared as previously described in Example 109 to afford (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(methylsulfonyl)phenyl)pyridin-2-yl)carbamate (25.6 mg, 75%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.34 (d, J = 5.2 Hz, 1H), 8.14 (s, 1H), 8.12 - 8.03 (m, 2H), 7.45 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 5.3 Hz, 1H), 3.97 (s,
 15 2H), 3.71 (s, 3H), 3.42 (s, 3H), 1.83 (dt, J = 12.2, 6.2 Hz, 1H), 1.49 - 1.37 (m, 2H), 1.17 (s, 3H), 0.94 (dd, J = 8.7, 6.6 Hz, 6H); LCMS (ESI) m/e 436.0 [(M+H) $^+$, calcd C₂₁H₃₀N₃O₅S, 436.2]; LC/MS retention time (method B): t_R = 1.52 min.

20

Example 114

(S)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(methylsulfonyl)phenoxy)pentan-2-amine

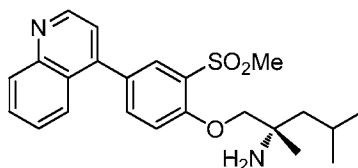


Prepared as described in Example 113 to afford (S)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(methylsulfonyl)phenoxy)pentan-2-amine (19 mg, 0.049
 25 mmol, 83%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.51 (d, J = 5.3 Hz, 1H), 8.17 - 8.10 (m, 2H), 7.59 (s, 1H), 7.52 - 7.46 (m, 1H), 7.43 (d, J = 9.2 Hz, 1H), 3.97 (s, 2H), 3.55 (s, 3H), 2.55 (s, 3H), 1.83 (dt, J = 13.0, 6.3 Hz, 1H), 1.50 - 1.37 (m, 2H), 1.17

(s, 3H), 0.94 (dd, $J = 8.8, 6.5$ Hz, 6H); LCMS (ESI) m/e 377.0 $[(M+H)^+]$, calcd $C_{20}H_{29}N_2O_3S$, 377.2]; LC/MS retention time (method B): $t_R = 1.32$ min.

Example 115

5 (S)-2,4-dimethyl-1-(2-(methylsulfonyl)-4-(quinolin-4-yl)phenoxy)pentan-2-amine

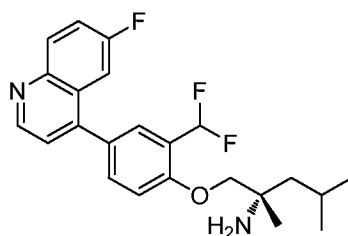


Prepared as described in Example 113 to afford (S)-2,4-dimethyl-1-(2-(methylsulfonyl)-4-(quinolin-4-yl)phenoxy)pentan-2-amine (12.2 mg, 0.029 mmol, 58%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.97 (d, $J = 4.4$ Hz, 1H), 8.14 (d, $J = 8.3$ Hz, 1H), 7.95 - 7.87 (m, 3H), 7.83 (t, $J = 7.7$ Hz, 1H), 7.65 (t, $J = 7.7$ Hz, 1H), 7.55 - 7.47 (m, 2H), 4.01 (s, 2H), 3.49 (s, 3H), 1.85 (dt, $J = 12.9, 6.5$ Hz, 1H), 1.53 - 1.39 (m, 2H), 1.19 (s, 3H), 0.97 (dd, $J = 8.4, 6.6$ Hz, 6H); LCMS (ESI) m/e 413.0 $[(M+H)^+]$, calcd $C_{23}H_{29}N_2O_3S$, 413.2]; LC/MS retention time (method B): $t_R = 1.41$ min.

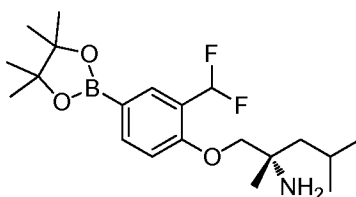
15

Example 116

(S)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



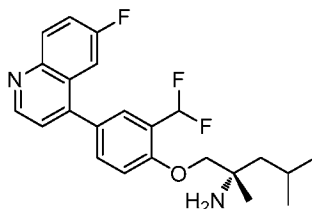
20



Part A: (S)-1-(2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-amine

To a 5 mL vial was added (S)-1-(4-bromo-2-(difluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (16.2 mg, 0.048 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (14.68 mg, 0.058 mmol), and potassium acetate (14.19 mg, 0.145 mmol) in dioxane (0.5 mL) to give a colorless suspension with nitrogen bubbling. PdCl₂(dppf) (1.058 mg, 1.446 μmol) was added under nitrogen. The vial was sealed and the mixture was heated at 80 °C for 4 h. LCMS showed most starting material was gone and several peaks. It was used directly in the next step.

10



Part B: (S)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

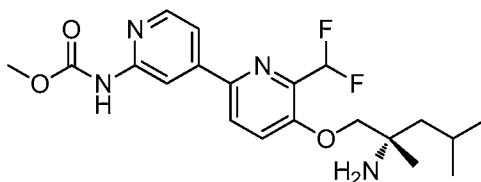
The mixture of (S)-1-(2-(difluoromethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-amine (18.40 mg, 0.048 mmol), 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, dichloromethane complex (2.74 mg, 3.36 μmol), Na₂CO₃ (0.096 mL, 0.192 mmol) and 4-chloro-6-fluoroquinoline (8.72 mg, 0.048 mmol) in dioxane (0.5 mL) (degassed) (previous vial) was heated at 120 °C for 16 h. The reaction mixture was diluted with ethyl acetate and dried (Na₂SO₄), filtered and concentrated. The residue was dissolved in MeOH and purified by prep-HPLC to afford (S)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (6.7 mg, 35% for two steps): ¹H NMR (500 MHz, DMSO-d₆) δ 8.95 (d, *J* = 4.5 Hz, 1H), 8.20 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.74 (ddd, *J* = 13.0, 8.0, 3.4 Hz, 2H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 4.4 Hz, 1H), 7.50 (dd, *J* = 10.3, 2.9 Hz, 1H), 7.44 - 7.17 (m, 2H), 3.61 (s, 2H), 1.82 (dq, *J* = 12.8, 6.4 Hz, 1H), 1.50 - 1.37 (m, 2H), 1.16 (s, 3H), 0.95 (dd, *J* = 10.2, 6.6 Hz, 6H); LCMS (ESI) *m/e* 403.0 [(M+H)⁺, calcd C₂₃H₂₆F₃N₂O, 403.2]; LC/MS retention time (method B): *t*_R = 1.78 min.

20

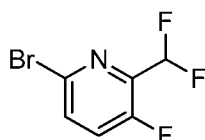
25

Example 117

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



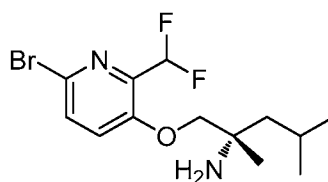
5



Part A: 6-bromo-2-(difluoromethyl)-3-fluoropyridine

To a 100 mL round-bottomed flask was added 6-bromo-3-fluoropicolinaldehyde (459.8 mg, 2.254 mmol) in CH₂Cl₂ (10 mL) to give a tan solution. After cooling to -20 °C, DAST (0.596 mL, 4.51 mmol) was added dropwise under nitrogen. The mixture was gradually warmed up to rt. The mixture was stirred at rt for 3 h. TLC (3/1 hexane/EtOAc) showed complete conversion to a less polar spot. The reaction was slowly quenched by saturated NaHCO₃ solution and diluted with ether. The layers were separated. The organic layer was washed with water, brine, dried and concentrated to 6-bromo-2-(difluoromethyl)-3-fluoropyridine (509 mg, 100%) as a tan solid: ¹H NMR (400 MHz, Chloroform-d) δ 7.65 (ddt, *J* = 8.6, 3.5, 1.0 Hz, 1H), 7.46 (t, *J* = 8.7 Hz, 1H), 6.73 (t, *J* = 53.4 Hz, 1H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -116.97, -127.89.

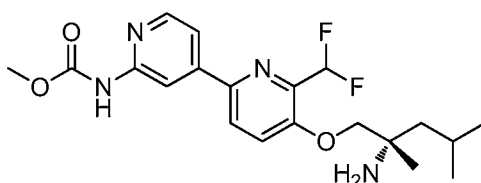
20



Part B: (S)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a 5 mL pressure bottle was added (*S*)-2-amino-2,4-dimethylpentan-1-ol (140 mg, 1.067 mmol) in tetrahydrofuran (1.3 mL) to give a colorless solution. Potassium *tert*-butoxide (1.280 mL, 1.280 mmol) (1.0 M in THF) was added

dropwise under nitrogen. After 5 min, 6-bromo-2-(difluoromethyl)-3-fluoropyridine (241 mg, 1.067 mmol) was added in one portion. The bottle was sealed and the mixture was stirred at 80 °C for 18 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with
 5 EtOAc. The combined organic solution was washed with brine, dried and concentrated to a tan oil (338 mg, 94%): ¹H NMR (400 MHz, Chloroform-d) δ 7.54 (dt, *J* = 9.0, 1.1 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 6.74 (t, *J* = 53.9 Hz, 1H), 3.79 (d, *J* = 1.7 Hz, 2H), 1.80 (dtd, *J* = 13.3, 6.7, 1.1 Hz, 1H), 1.54 (s, 2H), 1.52 - 1.47 (m, 2H), 1.25 (s, 3H), 1.00 (dd, *J* = 8.3, 6.6 Hz, 6H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -117.98.; LCMS (ESI) *m/e* 336.9 [(M+H)⁺, calcd C₁₃H₂₀BrF₂N₂O, 337.1]; LC/MS retention time (method B): *t*_R = 1.67 min.

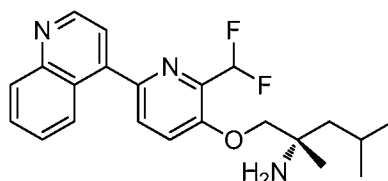


Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-
 15 *bipyridin]-2'-yl)carbamate*

To a 2 mL vial was added (*S*)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (28.4 mg, 0.084 mmol), (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (41.3 mg, 0.211 mmol), and Na₂CO₃ (0.126 mL, 0.253 mmol) in dioxane (0.6 mL) to give a colorless suspension
 20 under nitrogen. 1,1'-bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene (3.46 mg, 4.21 μmol) was added under nitrogen. The vial was sealed and heated at 100 °C (bath temp: 110 °C) for 3 h. The mixture was diluted with EtOAc and passed through a plug of Na₂SO₄. The organic solution was concentrated. The residue was purified twice by prep-HPLC to afford (*S*)-methyl (5-((2-amino-2,4-
 25 dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (12.6 mg, 37%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.50 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.67 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.22 (t, *J* = 53.6 Hz, 1H), 3.88 (s, 2H), 3.52 (s, 3H), 1.86 - 1.73 (m, 1H), 1.47 - 1.33 (m, 2H), 1.13 (s, 3H), 0.93 (dd, *J* = 10.0, 6.6 Hz, 6H); LCMS (ESI) *m/e* 409.0 (M+H)⁺, calcd C₂₀H₂₇F₂N₄O₃, 409.2]; LC/MS retention time (method B): *t*_R = 1.66 min.

Example 118

(*S*)-1-((2-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



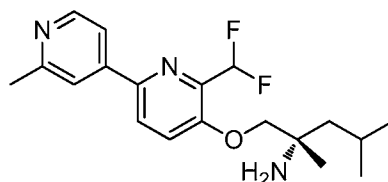
5

Prepared as described in Example 117 to afford (*S*)-1-((2-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (10.6 mg, 0.027 mmol, 60% yield for three steps): ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.01 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.64 (dd, *J* = 9.5, 6.0 Hz, 2H), 7.28 (t, *J* = 53.6 Hz, 1H), 3.53 (s, 2H), 1.83 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.50 - 1.37 (m, 2H), 1.16 (s, 3H), 0.95 (dd, *J* = 10.0, 6.7 Hz, 6H); LCMS (ESI) *m/e* 386.0 [(*M*+*H*)⁺, calcd C₂₂H₂₆F₂N₃O, 386.2]; LC/MS retention time (method B): *t*_R = 1.54 min.

15

Example 119

(*S*)-1-((6-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

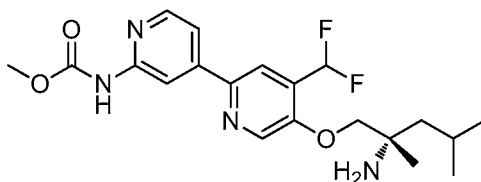


Prepared as described in Example 117 to afford (*S*)-1-((6-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (18.3 mg, 0.051 mmol, 92% yield for three steps): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.54 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 7.82 (d, *J* = 5.3 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.23 (t, *J* = 53.6 Hz, 1H), 3.89 (s, 2H), 2.56 (s, 3H), 1.81 (dq, *J* = 12.8, 6.5 Hz, 1H), 1.50 - 1.34 (m, 2H), 1.14 (s, 3H), 0.92 (dd, *J* = 10.5, 6.6 Hz, 6H); LCMS (ESI) *m/e* 350.0 [(*M*+*H*)⁺, calcd C₁₉H₂₆F₂N₃O, 350.2]; LC/MS retention time (method B): *t*_R = 1.45 min.

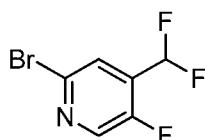
25

Example 120

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

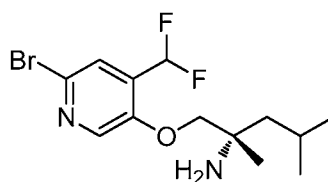


5

*Part A: 2-bromo-4-(difluoromethyl)-5-fluoropyridine*

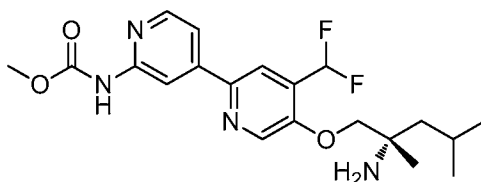
To a 100 mL round-bottomed flask was added 2-bromo-5-fluoroisonicotinaldehyde (605 mg, 2.97 mmol) in CH₂Cl₂ (12 mL) to give a tan solution. After cooling to -20 °C, DAST (0.705 mL, 5.34 mmol) was added dropwise under nitrogen. The mixture was gradually warmed up to rt. The mixture was stirred at rt for 3 h. TLC (3/1 hexane/EtOAc) showed complete conversion to a less polar spot. The reaction was slowly quenched by saturated NaHCO₃ solution and diluted with ether. The layers were separated. The organic layer was washed with water, brine, dried and concentrated to afford 2-bromo-4-(difluoromethyl)-5-fluoropyridine (639 mg, 95%) as a tan oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 8.39 (q, *J* = 1.2 Hz, 1H), 7.77 - 7.68 (m, 1H), 6.86 (t, *J* = 54.0 Hz, 1H); ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -117.92, -135.51.

20

*Part B: (S)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine*

To a 20 mL pressure bottle was added (*S*)-2-amino-2,4-dimethylpentan-1-ol (146 mg, 1.113 mmol) and 2-bromo-4-(difluoromethyl)-5-fluoropyridine (251 mg, 1.113 mmol) in tetrahydrofuran (1.5 mL) to give a tan solution. Potassium *tert*-

butoxide (1.335 mL, 1.335 mmol) (1.0 M in THF) was added dropwise under nitrogen. After 5 min stirring at rt, the bottle was sealed and the mixture was stirred at 80 °C for 18 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc. The combined
 5 organic solution was washed with brine, dried and concentrated to a tan oil (361 mg, 96%): ¹H NMR (400 MHz, Chloroform-d) δ 8.13 (s, 1H), 7.62 (s, 1H), 6.85 (t, *J* = 54.4 Hz, 1H), 3.87 (s, 2H), 1.80 (dtd, *J* = 13.2, 6.7, 1.0 Hz, 1H), 1.61 - 1.50 (m, 2H), 1.50 - 1.47 (m, 2H), 1.24 (s, 3H), 1.00 (dd, *J* = 7.4, 6.7 Hz, 6H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -119.58; LCMS (ESI) *m/e* 336.9 [(*M*+*H*)⁺, calcd C₁₃H₂₀BrF₂N₂O, 337.1]; LC/MS retention time (method B): *t_R* = 1.79 min.

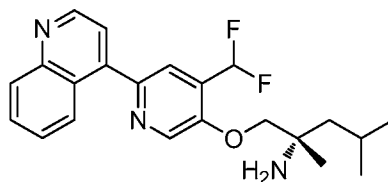


Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

15 Prepared as described in Example 117 to afford (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (2.5 mg, 0.006 mmol, 6% yield for three steps): ¹H NMR (500 MHz, DMSO-d₆) δ 8.71 (s, 1H), 8.53 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.08 (s, 1H), 7.71 (d, *J* = 5.2 Hz, 1H), 7.48 (t, *J* = 53.9 Hz, 1H), 4.12 (s, 2H), 3.71 (s, 3H), 1.82 (dt, *J* = 12.9, 6.4 Hz, 1H),
 20 1.53 (dd, *J* = 14.2, 5.3 Hz, 1H), 1.46 (dd, *J* = 14.2, 5.8 Hz, 1H), 1.22 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 408.9 (*M*+*H*)⁺, calcd C₂₀H₂₇F₂N₄O₃, 409.2]; LC/MS retention time (method B): *t_R* = 1.66 min.

Example 121

25 (S)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

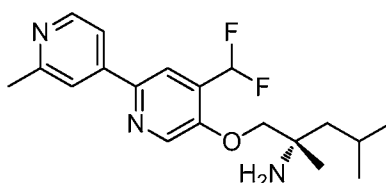


Prepared as described in Example 117 to afford (*S*)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (11.7 mg, 0.030 mmol, 69% yield for three steps): ¹H NMR (500 MHz, DMSO-d₆) δ 9.00 (d, *J* = 4.4 Hz, 1H), 8.78 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.69 - 7.60 (m, 2H), 7.39 (t, *J* = 53.8 Hz, 1H), 4.06 (s, 2H), 1.84 (dt, *J* = 12.9, 6.3 Hz, 1H), 1.51 - 1.37 (m, 2H), 1.17 (s, 3H), 0.96 (dd, *J* = 11.7, 6.7 Hz, 6H); LCMS (ESI) *m/e* 386.0 [(M+H)⁺, calcd C₂₂H₂₆F₂N₃O, 386.2]; LC/MS retention time (method B): *t*_R = 1.58 min.

10

Example 122

(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



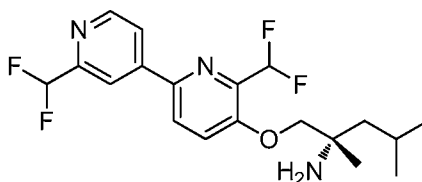
Prepared as described in Example 117 to afford (*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (13.6 mg, 0.039 mmol, 74% yield for three steps): ¹H NMR (500 MHz, DMSO-d₆) δ 8.68 (s, 1H), 8.54 (d, *J* = 5.3 Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 5.2 Hz, 1H), 7.39 (t, *J* = 53.9 Hz, 1H), 4.06 (s, 2H), 2.56 (s, 3H), 1.81 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.45 (qd, *J* = 14.2, 5.7 Hz, 2H), 1.18 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 350.0 [(M+H)⁺, calcd C₁₉H₂₆F₂N₃O, 350.2]; LC/MS retention time (method B): *t*_R = 1.46 min.

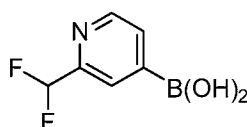
20

Example 123

(*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

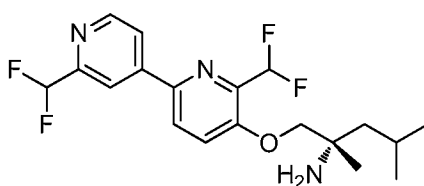
25





Part A: (2-(difluoromethyl)pyridin-4-yl)boronic acid

To a 20 mL vial was added 4-chloro-2-(difluoromethyl)pyridine hydrochloride (180 mg, 0.900 mmol), hypodiboric acid (121 mg, 1.350 mmol), 2-
 5 (dicyclohexylphosphino))-2',4',6'-triisopropylbiphenyl (8.58 mg, 0.018 mmol), Xphos precatalyst (7.08 mg, 9.00 μ mol) and potassium acetate (265 mg, 2.70 mmol) in ethanol (8.5 mL) to give a tan suspension (degassed before adding agents). The bottle was capped and heated at 80 °C for 1.5 h. LCMS showed the consumption of the starting material and formation of a new spot: (2-(difluoromethyl)pyridin-4-yl)boronic acid. The mixture was divided into parts and directly used in the next step
 10 of different reactions.



Part B: (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 15 *dimethylpentan-2-amine*

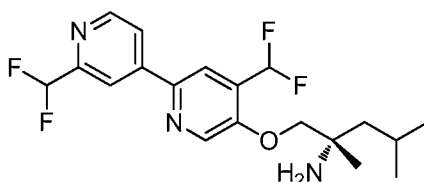
To a 5 mL vial was added (2-(difluoromethyl)pyridin-4-yl)boronic acid (25.9 mg, 0.15 mmol) was added potassium phosphate tribasic (1 mL, 0.500 mmol). After degassing for 5 min, Xphos precatalyst (4 mg, 5.08 μ mol) and (S)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (26.5 mg, 0.079
 20 mmol) and tetrahydrofuran (1mL) were added. The vial was sealed and heated at 80 °C overnight for 18 h. Volatiles were blown off. The residue was partitioned between EtOAc and water. The organic layer was dried, filtered and concentrated. The residue was dissolved in MeOH and purified by prep-HPLC to afford (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine
 25 (29.8 mg, 98%) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.79 (d, *J* = 5.2 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.32 (s, 1H), 8.21 (d, *J* = 5.1 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.31 (t, *J* = 53.5 Hz, 1H), 7.04 (t, *J* = 54.9 Hz, 1H), 3.96 (s, 2H), 3.46 (s, 2H), 1.80 (dp, *J* = 12.5, 6.7, 6.3 Hz, 1H), 1.45 (qd, *J* = 14.1, 5.6 Hz, 2H),

1.17 (s, 3H), 0.92 (dd, $J = 13.6, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -115.43 (d, $J = 55.2$ Hz), -117.78 - -119.55 (m); LCMS (ESI) m/e 386.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{19}\text{H}_{24}\text{F}_4\text{N}_3\text{O}$, 386.2]; LC/MS retention time (method B): $t_R = 1.85$ min.

5

Example 124

(*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



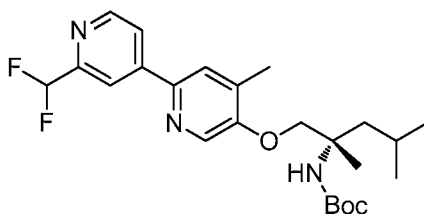
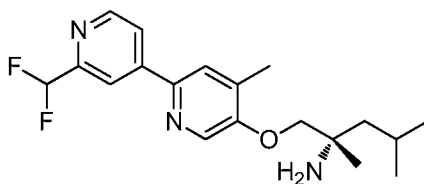
Prepared as described in Example 123 to afford (*S*)-1-((2',4-

10 bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (25.9 mg, 0.067 mmol, 77% yield) as a colorless solid. ^1H NMR (500 MHz, DMSO- d_6) δ 8.79 (d, $J = 5.2$ Hz, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 8.25 (d, $J = 5.1$ Hz, 1H), 7.35 (t, $J = 53.9$ Hz, 1H), 7.04 (t, $J = 54.9$ Hz, 1H), 4.03 (s, 2H), 1.81 (dt, $J = 12.8, 6.4$ Hz, 1H), 1.48 - 1.33 (m, 2H), 1.14 (s, 3H), 0.93 (dd, $J = 12.3, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -115.44 (d, $J = 54.7$ Hz), -116.34 - -119.67 (m); LCMS (ESI) m/e 386.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{19}\text{H}_{24}\text{F}_4\text{N}_3\text{O}$, 386.2]; LC/MS retention time (method B): $t_R = 1.83$ min.

15

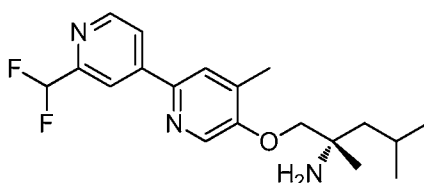
Example 125

20 (*S*)-1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-tert-butyl (1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 123 to afford (*S*)-*tert*-butyl (1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (38.5 mg, 0.086 mmol, 80% yield) as a colorless solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.71 (d, *J* = 5.2 Hz, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 1.7 Hz, 1H), 7.98 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.66 (s, 1H), 6.72 (t, *J* = 55.5 Hz, 1H), 4.63 (s, 1H), 4.32 (d, *J* = 8.7 Hz, 1H), 4.14 (d, *J* = 8.8 Hz, 1H), 2.36 (s, 3H), 1.96 - 1.77 (m, 2H), 1.65 - 1.54 (m, 1H), 1.44 (s, 3H), 1.42 (s, 9H), 1.01 (dd, *J* = 6.6, 3.5 Hz, 6H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -115.81; LCMS (ESI) *m/e* 450.1 [(M+H)⁺, calcd C₂₄H₃₄F₂N₃O₃, 450.2]; LC/MS retention time (method B): *t_R* = 2.31 min.

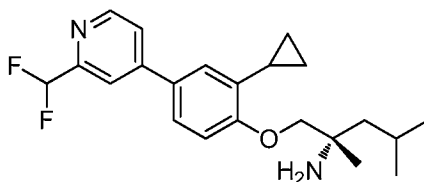


Part B: (S)-1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

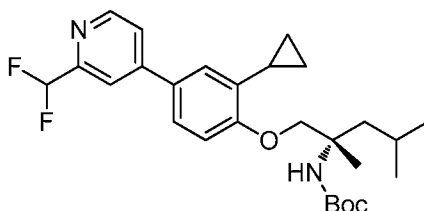
Prepared as previously described in Example 7, Part B (34.9 mg, 100%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.76 (d, *J* = 5.1 Hz, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 8.22 - 8.15 (m, 1H), 8.12 (s, 1H), 7.03 (t, *J* = 55.0 Hz, 1H), 4.13 - 4.00 (m, 2H), 2.36 (s, 3H), 1.83 (dp, *J* = 12.7, 6.5 Hz, 1H), 1.60 (dd, *J* = 14.1, 5.5 Hz, 1H), 1.52 (dd, *J* = 14.1, 5.6 Hz, 1H), 1.27 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -115.37 (d, *J* = 54.8 Hz); LCMS (ESI) *m/e* 350.0 [(M+H)⁺, calcd C₁₉H₂₆F₂N₃O, 350.2]; LC/MS retention time (method B): *t_R* = 1.80 min.

Example 126

(*S*)-1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



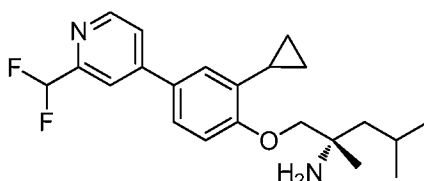
5



Part A: (S)-tert-butyl (1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 123 to afford (*S*)-tert-butyl (1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (31.4 mg, 0.066 mmol, 79% yield) as a colorless solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.65 (d, *J* = 5.1 Hz, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.47 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.23 (d, *J* = 2.3 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 6.71 (t, *J* = 55.5 Hz, 1H), 4.73 (s, 1H), 4.21 (d, *J* = 8.8 Hz, 1H), 4.05 (d, *J* = 8.8 Hz, 1H), 2.19 (tt, *J* = 8.6, 5.4 Hz, 1H), 1.87 (ddt, *J* = 13.1, 11.4, 6.8 Hz, 2H), 1.72 - 1.62 (m, 1H), 1.47 (s, 3H), 1.43 (s, 9H), 1.01 (dt, *J* = 5.5, 2.7 Hz, 8H), 0.74 (td, *J* = 5.7, 4.0 Hz, 2H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -115.77; LCMS (ESI) *m/e* 475.0 [(*M*+*H*)⁺, calcd C₂₇H₃₇F₂N₂O₃, 475.3]; LC/MS retention time (method B): *t*_R = 2.48 min.

20

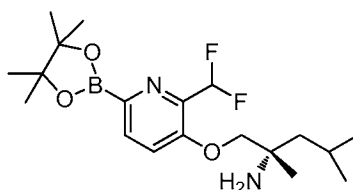
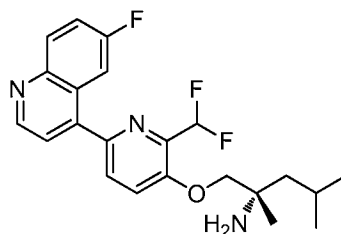


Part B: (S)-1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7, Part B (25.8 mg, 100%) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.66 (d, *J* = 5.3 Hz, 1H), 7.94 (s, 1H), 7.86 (d, *J* = 5.3 Hz, 1H), 7.66 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.11 - 6.84 (m, 2H), 3.90 - 3.79 (m, 2H), 2.26 (td, *J* = 8.5, 4.2 Hz, 1H), 1.82 (hept, *J* = 6.4 Hz, 1H), 1.50 (qd, *J* = 14.1, 5.6 Hz, 2H), 1.21 (s, 3H), 0.98 - 0.88 (m, 8H), 0.86 - 0.73 (m, 2H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -115.05 (d, *J* = 54.9 Hz); LCMS (ESI) *m/e* 375.0 [(M+H)⁺, calcd C₂₂H₂₉F₂N₂O, 375.2]; LC/MS retention time (method B): *t*_R = 1.97 min.

Example 127

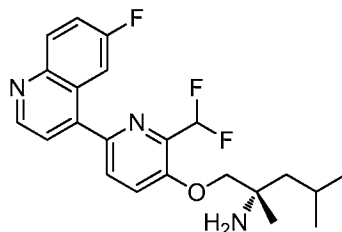
(S)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-1-((2-(difluoromethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a 5 mL vial was added *(S)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine* (79.5 mg, 0.236 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (71.8 mg, 0.283 mmol), and potassium acetate (69.4 mg, 0.707 mmol) in dioxane (2.4 mL) to give a colorless suspension with nitrogen bubbling. PdCl₂(dppf) (5.18 mg, 7.07 μmol) was added under nitrogen. The vial was sealed and the mixture was heated at 80 °C for 20 h. LC/MS

showed complete conversion to a new peak. It was divided into parts and used directly in the next step. LC/MS retention time (method B): $t_R = 1.52$ min.

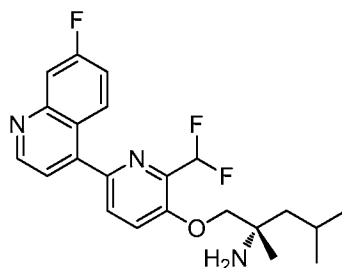


5 *Part B: (S)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine*

Prepared as previously described in Example 116 to afford (S)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (5.3 mg, 16% for 2 steps) as a colorless solid. ^1H NMR (400MHz, CHLOROFORM-d) δ 8.97 (d, $J=4.5$ Hz, 1H), 8.19 (dd, $J=9.3$, 5.5 Hz, 1H), 7.85 (dd, $J=10.4$, 2.9 Hz, 1H), 7.73 (d, $J=8.5$ Hz, 1H), 7.59 - 7.43 (m, 3H), 7.09 - 6.72 (t, $J=54.0$ Hz, 1H), 4.01 - 3.84 (m, 2H), 1.91 - 1.78 (m, 1H), 1.61 - 1.49 (m, 2H), 1.31 (s, 3H), 1.03 (app t, $J=7.0$ Hz, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 404.0 $[(M+H)^+]$, calcd $\text{C}_{22}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 404.2]; LC/MS retention time
10
15 (method B): $t_R = 1.81$ min.

Example 128

(S)-1-((2-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

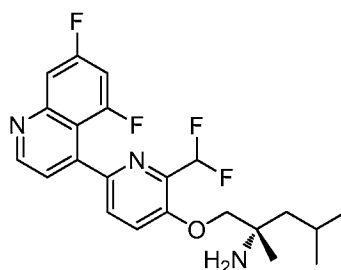


20 Prepared as previously described in Example 116 to afford (S)-1-((2-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (11.1 mg, 35% for 2 steps) as a colorless solid. ^1H NMR (400MHz, CHLOROFORM-d) δ 8.98 (d, $J=4.5$ Hz, 1H), 8.21 (dd, $J=9.3$, 6.0 Hz, 1H), 7.81 (dd, $J=9.9$, 2.6 Hz, 1H), 7.72 (d, $J=8.5$ Hz, 1H), 7.50 (d, $J=8.8$ Hz, 1H), 7.45 (d, $J=4.5$ Hz,
25

1H), 7.35 (ddd, $J=9.3, 8.0, 2.8$ Hz, 1H), 6.98 (t, $J=55.0$ Hz, 1H), 3.98 (s, 2H), 1.85 (tt, $J=12.7, 6.4$ Hz, 1H), 1.68 - 1.56 (m, 2H), 1.36 (s, 3H), 1.03 (d, $J=6.8$ Hz, 3H), 1.01 (d, $J=6.8$ Hz, 3H), two exchangeable protons not observed; LCMS (ESI) m/e 404.0 $[(M+H)^+]$, calcd $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): $t_R =$
5 1.68 min.

Example 129

(*S*)-1-((2-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



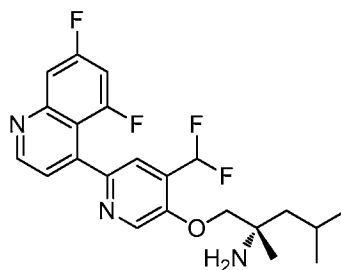
10

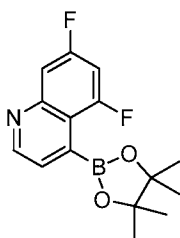
Prepared as previously described in Example 16 to afford (*S*)-1-((2-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (25.9 mg, 75% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 9.13 - 9.02 (m, 1H), 7.93 - 7.73 (m, 3H), 7.56 (dt, $J = 23.8, 6.1$ Hz, 2H), 7.38 - 7.09 (m, 1H), 3.95 (d, $J = 22.2$ Hz, 2H), 1.84 (dt, $J = 18.4, 6.3$ Hz, 1H), 1.45 (dtd, $J = 23.9, 14.0, 11.7, 5.4$ Hz, 2H), 1.27 - 1.14 (m, 3H), 0.96 (ddd, $J = 23.9, 13.5, 6.6$ Hz, 6H); LCMS (ESI) m/e 421.9 $[(M+H)^+]$, calcd $C_{22}H_{24}F_4N_3O$, 422.2]; LC/MS retention time (method B): $t_R = 1.82$ min.

20

Example 130

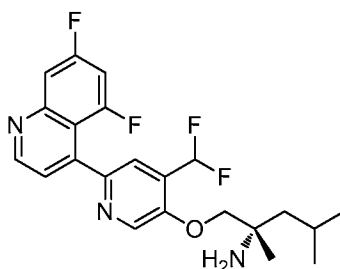
(*S*)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: 5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

Prepared as previously described in Example 127. Obtained 5,7-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline which was divided into parts
5 and used directly in the next step. LC/MS retention time (method A): $t_R = 1.93$ min.



Part B: (S)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

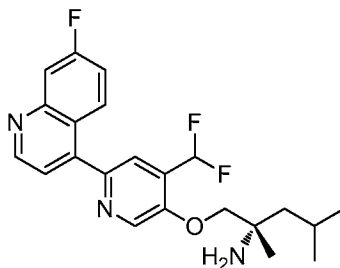
Prepared as previously described in Example 16 to afford (S)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (14.7 mg, 49% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 9.04 (d, $J = 4.7$ Hz, 1H), 8.62 (d, $J = 5.7$ Hz, 1H), 7.80 (d, $J = 9.6$ Hz, 1H), 7.75 (d, $J = 6.5$ Hz, 1H), 7.56 (qd, $J = 8.5, 7.9, 4.9$ Hz, 2H), 7.36 (t, $J = 53.9$ Hz, 1H), 4.01 (s, 2H), 1.82 (q, $J = 6.5$ Hz, 1H), 1.43 (qd, $J = 14.0, 5.9$ Hz, 2H), 1.16 (s, 3H), 0.94 (dd, $J = 14.6, 6.7$ Hz, 6H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -102.43 (d, $J = 9.6$ Hz), -107.91 (d, $J = 9.0$ Hz), -116.03 - -119.87 (m); LCMS (ESI) m/e 422.0 $[(M+H)^+]$, calcd $\text{C}_{22}\text{H}_{24}\text{F}_4\text{N}_3\text{O}$, 422.2; LC/MS retention time (method B): $t_R = 1.88$ min.

20

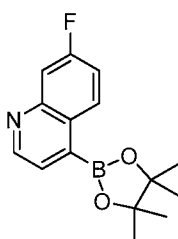
25

Example 131

(*S*)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

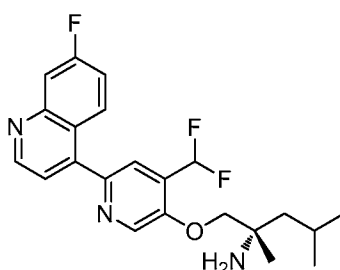


5



Part A: 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

Prepared as previously described in Example 127. Obtained 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline which was divided into parts
10 and used directly in the next step. LC/MS retention time (method A): t_R = 1.19 min.



Part B: (S)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

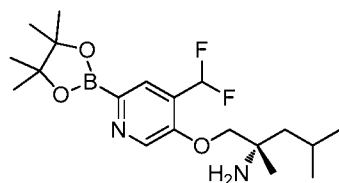
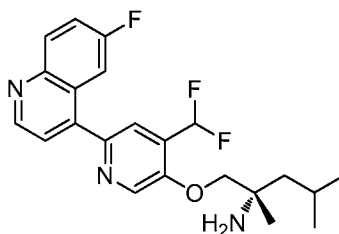
15 Prepared as previously described in Example 16 to afford (*S*)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (11.1 mg, 39% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 9.02 (d, J = 4.3 Hz, 1H), 8.77 (s, 1H), 8.30 (ddd, J = 9.0, 6.3, 2.4 Hz, 1H), 7.90 (s, 1H), 7.86 (dd, J = 10.2, 2.7 Hz, 1H), 7.67 (d, J = 4.3 Hz, 1H), 7.58 (td, J = 8.8, 2.7 Hz, 1H), 7.37 (t, J = 53.9 Hz, 1H), 4.05 (s, 2H), 1.83 (p, J = 6.5 Hz, 1H), 1.43
20 (qd, J = 14.0, 5.4 Hz, 2H), 1.16 (s, 3H), 0.95 (ddd, J = 13.9, 6.8, 2.1 Hz, 6H); ^{19}F

NMR (376 MHz, DMSO- d_6) δ -110.25 , -115.90 - -119.14 (m); LCMS (ESI) m/e 404.0 $[(M+H)^+]$, calcd $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.78 min.

5

Example 132

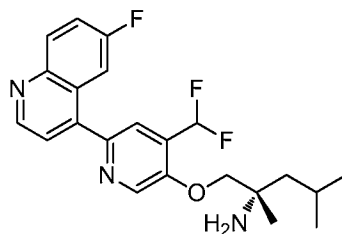
(*S*)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



10

Part A: (S)-1-((4-(difluoromethyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a 5 mL vial was added (*S*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (82.5 mg, 0.245 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (74.6 mg, 0.294 mmol), and potassium acetate (72.0 mg, 0.734 mmol) in dioxane (2.4 mL) to give a colorless suspension with nitrogen bubbling. $PdCl_2(dppf)$ (5.37 mg, 7.34 μ mol) was added under nitrogen. The vial was sealed and the mixture was heated at 80 °C for 20 h. LCMS showed mainly the starting material (dark red color mixture). The temperature was raised to 100 °C. After 4 h, LCMS showed a little better conversion. The reaction continued for another 16 h at 100 °C. LCMS showed better conversion but there was still some starting material left. The temperature was raised to 110 °C and the reaction continued for 5 h. LCMS showed only a little starting material left. The reaction continued at 110 °C for another 5 h. After cooling down, the reaction mixture was divided into parts and used directly in the next step.

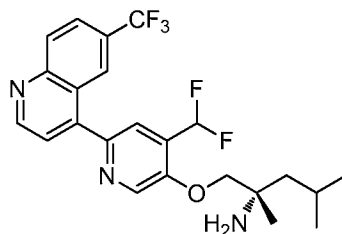


Part B: (S)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 116 to afford (S)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (1.6 mg, 5% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 8.99 (d, $J = 4.4$ Hz, 1H), 8.80 (s, 1H), 8.20 (dd, $J = 9.3, 5.6$ Hz, 1H), 8.01 (dd, $J = 11.0, 2.9$ Hz, 1H), 7.94 (s, 1H), 7.79 - 7.70 (m, 2H), 7.40 (t, $J = 53.9$ Hz, 1H), 4.09 (s, 2H), 1.84 (dt, $J = 12.8, 6.5$ Hz, 1H), 1.46 (qd, $J = 14.0, 5.6$ Hz, 2H), 1.19 (s, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); ^{19}F NMR (376 MHz, DMSO- d_6) δ -112.45, -118.42 (dd, $J = 134.0, 57.0$ Hz); LCMS (ESI) m/e 404.0 $[(M+H)^+]$, calcd $\text{C}_{22}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 404.2]; LC/MS retention time (method B): $t_R = 1.79$ min.

Example 133

((S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

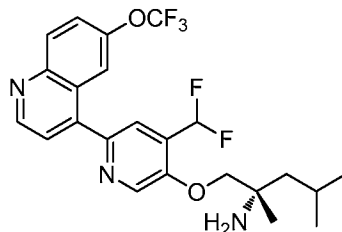


Prepared as previously described in Example 132 to afford ((S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (2.1 mg, 6% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 9.17 (d, $J = 4.4$ Hz, 1H), 8.85 (s, 1H), 8.75 (s, 1H), 8.34 (d, $J = 8.8$ Hz, 1H), 8.08 (dd, $J = 8.8, 2.1$ Hz, 1H), 8.02 (s, 1H), 7.88 (d, $J = 4.3$ Hz, 1H), 7.43 (t, $J = 53.9$ Hz, 1H), 4.13 (d, $J = 3.0$ Hz, 2H), 1.84 (p, $J = 6.2$ Hz, 1H), 1.57 - 1.41 (m, 2H), 1.21 (s, 3H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.5$ Hz, 3H); LCMS

(ESI) m/e 454.0 $[(M+H)^+]$, calcd $C_{23}H_{25}F_5N_3O$, 454.2]; LC/MS retention time (method B): t_R = 2.02 min.

Example 134

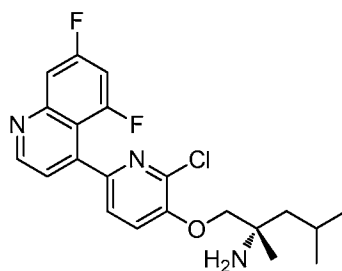
5 (S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethoxy)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

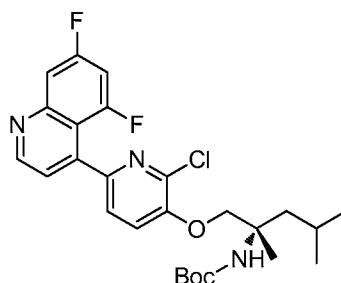


Prepared as previously described in Example 132 to afford (S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethoxy)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (1.5 mg, 4% for 2 steps) as a colorless solid. ^1H NMR (600 MHz, DMSO- d_6) δ 9.07 (d, J = 4.4 Hz, 1H), 8.80 (s, 1H), 8.29 (s, 1H), 8.27 (d, J = 9.2 Hz, 1H), 7.97 (s, 1H), 7.83 (dd, J = 8.7, 3.2 Hz, 2H), 7.38 (t, J = 53.9 Hz, 1H), 4.06 (s, 2H), 1.84 (dt, J = 12.7, 6.3 Hz, 1H), 1.42 (qd, J = 14.0, 5.6 Hz, 2H), 1.16 (s, 3H), 0.96 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); LCMS (ESI) m/e 470.0
 15 $[(M+H)^+]$, calcd $C_{23}H_{25}F_5N_3O_2$, 470.2]; LC/MS retention time (method B): t_R = 2.00 min.

Example 135

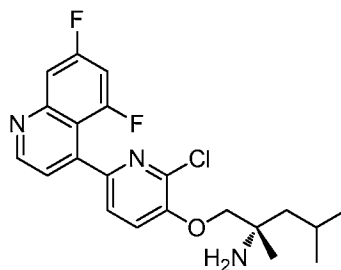
20 (S)-1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: (S)-tert-butyl 1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ylcarbamate

Prepared as previously described in Example 66. The intermediates were as described in Example 66 and Example 130 to afford (S)-tert-butyl 1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ylcarbamate (12.1 mg, 34%) as a colorless solid. ¹H NMR (400 MHz, Chloroform-d) δ 8.97 (d, *J* = 4.4 Hz, 1H), 7.68 (ddd, *J* = 9.5, 2.6, 1.5 Hz, 1H), 7.42 - 7.32 (m, 3H), 7.05 (ddd, *J* = 11.5, 8.8, 2.6 Hz, 1H), 4.64 (s, 1H), 4.37 (d, *J* = 8.9 Hz, 1H), 4.18 (d, *J* = 8.9 Hz, 1H), 1.96 (dd, *J* = 13.9, 6.4 Hz, 1H), 1.87 (ddd, *J* = 13.1, 6.5, 4.9 Hz, 1H), 1.58 (dd, *J* = 13.9, 4.9 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 9H), 1.04 (s, 3H), 1.02 (s, 3H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -102.47, -107.56.; LCMS (ESI) *m/e* 506.0 [(M+H)⁺, calcd C₂₆H₃₁ClF₂N₃O₃, 506.2]; LC/MS retention time (method B): *t_R* = 2.36 min.



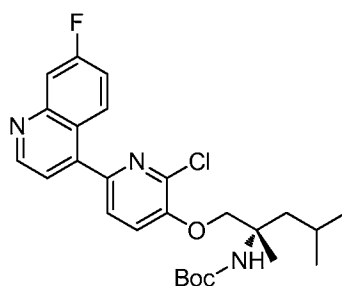
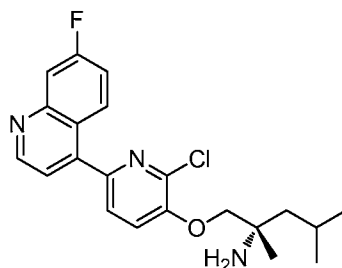
Part B: (S)-1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7, Part B to afford (S)-1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (10.6 mg, 100%) as a colorless solid. ¹H NMR (400MHz, CHLOROFORM-d) δ 8.97 (d, *J*=4.3 Hz, 1H), 7.77 - 7.62 (m, 1H), 7.40 (d, *J*=4.3 Hz, 1H), 7.38 - 7.34 (m, 1H), 7.33 - 7.28 (m, 1H), 7.05 (ddd, *J*=11.6, 8.8, 2.6 Hz, 1H), 3.93 - 3.84 (m, 2H), 1.92 - 1.73 (m, 1H), 1.66 - 1.50 (m, 2H), 1.32 (s, 3H), 1.04 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.5 Hz, 3H), two exchangeable protons not observed; ¹⁹F NMR (376 MHz, DMSO-d₆) δ

-101.38 - -103.03 (m), -105.03 - -107.99 (m); LCMS (ESI) m/e 405.9 $[(M+H)^+]$, calcd $C_{21}H_{23}ClF_2N_3O$, 406.1]; LC/MS retention time (method B): t_R = 1.84 min.

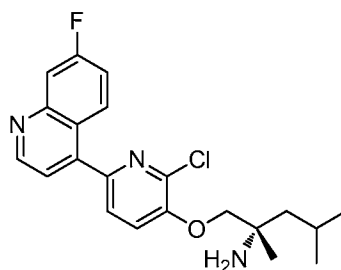
Example 136

- 5 (S)-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



- 10 *Part A: (S)-tert-butyl (1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Prepared as previously described in Example 66. The intermediates were as described in Example 66 and Example 131 to afford (S)-tert-butyl (1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (12.4 mg, 36%) as a colorless solid. ^1H NMR (400 MHz, Chloroform-d) δ 8.98 (d, J = 4.5 Hz, 1H), 8.24 (dd, J = 9.4, 6.1 Hz, 1H), 7.81 (dd, J = 9.9, 2.6 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.49 - 7.43 (m, 2H), 7.37 (ddd, J = 9.3, 8.0, 2.7 Hz, 1H), 4.64 (s, 1H), 4.41 (d, J = 9.0 Hz, 1H), 4.21 (d, J = 9.0 Hz, 1H), 2.01 - 1.82 (m, 2H), 1.58 (dd, J = 13.9, 5.0 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 9H), 1.05 (s, 3H), 1.03 (s, 3H); ^{19}F NMR (376 MHz, Chloroform-d) δ -109.85; LCMS (ESI) m/e 488.0 $[(M+H)^+]$, calcd $C_{26}H_{32}ClFN_3O_3$, 488.2]; LC/MS retention time (method B): t_R = 2.28 min.

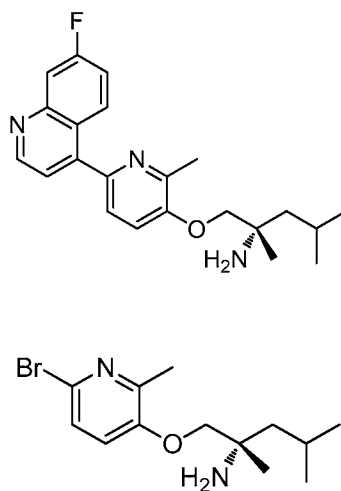


Part B: *(S)*-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7, Part B to afford *(S)*-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (11.1 mg, 100%) as a colorless solid. ¹H NMR (600 MHz, DMSO-d₆) δ 9.01 (d, *J* = 4.4 Hz, 1H), 8.32 (dd, *J* = 9.4, 6.1 Hz, 1H), 7.88 - 7.77 (m, 3H), 7.63 (d, *J* = 4.2 Hz, 1H), 7.60 (td, *J* = 8.8, 2.7 Hz, 1H), 3.98 - 3.89 (m, 2H), 1.85 (dq, *J* = 12.8, 6.4 Hz, 1H), 1.50 - 1.40 (m, 2H), 1.18 (s, 3H), 0.95 (dd, *J* = 7.5, 5.4 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -110.18; LCMS (ESI) *m/e* 388.0 [(M+H)⁺, calcd C₂₁H₂₄ClFN₃O, 388.2]; LC/MS retention time (method B): *t*_R = 1.76 min.

Example 137

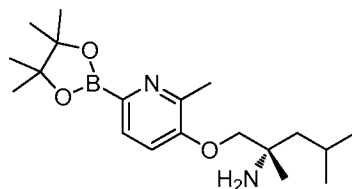
(S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: *(S)*-1-((6-bromo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

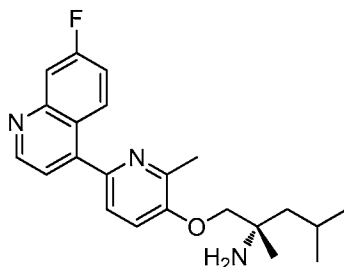
To a 20 mL pressure bottle was added *(S)*-2-amino-2,4-dimethylpentan-1-ol (214.8 mg, 1.637 mmol) in tetrahydrofuran (2.2 mL) to give a colorless solution. Potassium *tert*-butoxide (2.128 mL, 2.128 mmol) (1.0 M in THF) was added

dropwise under nitrogen. After 5 min, 6-bromo-3-fluoro-2-methylpyridine (311 mg, 1.637 mmol) was added in one portion. The bottle was sealed and the mixture was stirred at 80 °C for 20 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried and concentrated to a tan oil. It was purified by silica gel chromatography up to 10% MeOH (2N NH₃) in CH₂Cl₂ to afford (*S*)-1-((6-bromo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (220 mg, 45% with one unknown impurity-likely substitution at Br). LCMS (ESI) *m/e* 283.9 [(M-NH₂)⁺, calcd C₁₃H₁₉BrNO, 284.1]; LC/MS retention time (method B): *t*_R = 1.70 min (impurity: 1.81 min).



Part B: (S)-2,4-dimethyl-1-((2-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)oxy)pentan-2-amine

To a 5 mL vial was added (*S*)-1-((6-bromo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (89.5 mg, 0.267 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (81 mg, 0.321 mmol), and potassium acetate (79 mg, 0.802 mmol) in dioxane (2.8 mL) to give a colorless suspension with nitrogen bubbling. PdCl₂(dppf) (5.87 mg, 8.02 μmol) was added under nitrogen. The vial was sealed and the mixture was heated at 80 °C for 18 h. LCMS showed there was substantial amount of starting material. The reaction mixture was heated at 100 °C for 4 h. LCMS showed the majority of starting material was gone (the side product from previous reaction remained). It was divided into parts and used directly in the next step.



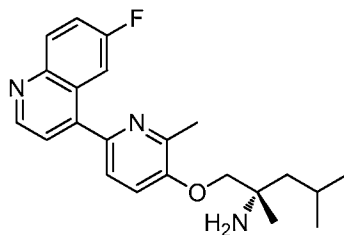
Part C: (S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 132 to afford (S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (1.0 mg, 3%) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.99 (d, *J* = 4.5 Hz, 1H), 8.37 (dd, *J* = 9.3, 6.4 Hz, 1H), 7.84 (dd, *J* = 10.4, 2.7 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.62 - 7.54 (m, 3H), 3.98 (s, 2H), 2.57 (s, 3H), 1.90 - 1.80 (m, 1H), 1.61 (d, *J* = 5.3 Hz, 1H), 1.53 (dd, *J* = 14.0, 5.5 Hz, 1H), 1.30 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H). LCMS (ESI) *m/e* 368.2 [(M+H)⁺, calcd C₂₂H₂₇FN₃O, 368.2]

10

Example 138

(S)-1-((6-(6-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



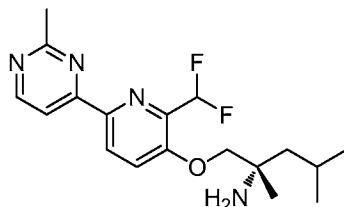
Prepared as previously described in Example 132 with intermediate from Example 137 to afford (S)-1-((6-(6-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (1.5 mg, 3%, 64% purity by analytical HPLC): ¹H NMR (500MHz, DMSO-d₆) δ 8.96 (d, *J*=4.4 Hz, 1H), 8.17 (dd, *J*=9.4, 5.7 Hz, 1H), 8.07 (dd, *J*=10.8, 2.8 Hz, 1H), 7.78 - 7.51 (m, 5H), 6.70 (dd, *J*=8.8, 2.6 Hz, 1H), 3.93 - 3.77 (m, 2H), 2.55 (s, 3H), 1.87 - 1.72 (m, 1H), 1.58 - 1.30 (m, 2H), 1.15 (s, 3H), 1.00 - 0.83 (m, 6H) LCMS (ESI) *m/e* 368.2 [(M+H)⁺, calcd C₂₂H₂₇FN₃O, 368.2].

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Example 139

(S)-1-((2-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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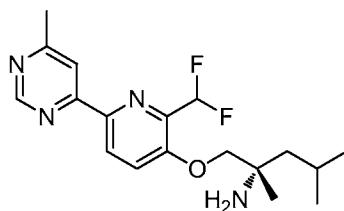


Prepared as previously described in Example 127 with intermediate as described in Example 127 and 4-bromo-2-methylpyrimidine to afford (*S*)-1-((2-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (15.9 mg, 45%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.82 (d, *J* = 5.2 Hz, 1H), 8.57 (d, *J* = 8.9 Hz, 1H), 8.07 (d, *J* = 5.3 Hz, 1H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.26 (t, *J* = 53.6 Hz, 1H), 3.92 (s, 2H), 2.71 (s, 3H), 1.81 (dd, *J* = 12.9, 6.6 Hz, 1H), 1.47 - 1.36 (m, 2H), 1.15 (s, 3H), 0.93 (dd, *J* = 11.0, 6.8 Hz, 6H); LCMS (ESI) *m/e* 373.1 [(M+Na)⁺, calcd C₁₈H₂₄F₂N₄NaO, 373.2]; LC/MS retention time (method B): *t*_R = 1.73 min.

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Example 140

(*S*)-1-((2-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

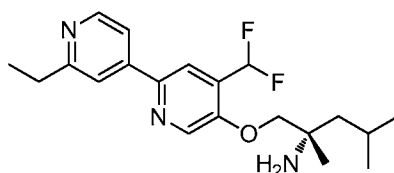


Prepared as previously described in Example 127 with intermediate as described in Example 127 and 4-bromo-6-methylpyrimidine to afford (*S*)-1-((2-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (3.5 mg, 6.8%): ¹H NMR (400MHz, CHLOROFORM-d) δ 9.11 (d, *J*=1.3 Hz, 1H), 8.58 (d, *J*=8.8 Hz, 1H), 8.21 (s, 1H), 7.43 (d, *J*=8.8 Hz, 1H), 7.10 - 6.72 (t, *J*=53.0 Hz, 1H), 3.96 (s, 2H), 2.63 (s, 3H), 1.88 - 1.75 (m, 1H), 1.66 - 1.52 (m, 2H), 1.26 (s, 3H), 1.01 (d, *J*=6.5 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H), two exchangeable protons not observed; LCMS (ESI) *m/e* 334.1 [(M-NH₂)⁺, calcd C₁₈H₂₂F₂N₃O, 334.2]; LC/MS retention time (method B): *t*_R = 1.78 min.

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Example 141

(*S*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



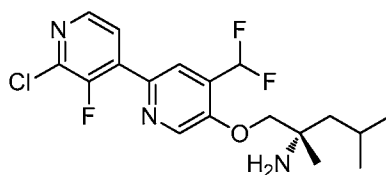
25

Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-ethylpyridin-4-yl)boronic acid to afford (*S*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (8.0 mg, 39%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.67 (s, 1H), 8.57 (d, *J* = 5.2 Hz, 1H), 8.20 (s, 1H), 7.93 (s, 1H), 7.85 (dd, *J* = 5.2, 1.6 Hz, 1H), 7.34 (t, *J* = 53.9 Hz, 1H), 4.01 (s, 2H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.80 (dq, *J* = 12.5, 6.2 Hz, 1H), 1.47 - 1.35 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.14 (s, 3H), 0.93 (dd, *J* = 12.6, 6.6 Hz, 6H); LCMS (ESI) *m/e* 364.2 [(*M*+H)⁺, calcd C₂₀H₂₈F₂N₃O, 364.2]; LC/MS retention time (method B): *t*_R = 1.54 min.

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Example 142

(*S*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

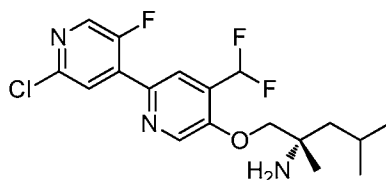


Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-chloro-3-fluoro-pyridin-4-yl)boronic acid to afford (*S*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (10.8 mg, 13%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.76 (s, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 8.05 (s, 1H), 7.97 (t, *J* = 5.3 Hz, 1H), 7.37 (t, *J* = 53.9 Hz, 1H), 4.03 (s, 2H), 1.81 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.45 - 1.35 (m, 2H), 1.14 (s, 3H), 0.93 (dd, *J* = 12.4, 6.7 Hz, 7H); LCMS (ESI) *m/e* 371.1 [(*M*-NH₂)⁺, calcd C₁₈H₁₉ClF₃N₂O, 371.1]; LC/MS retention time (method B): *t*_R = 1.98 min.

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Example 143

(*S*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



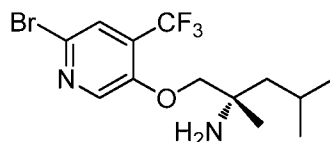
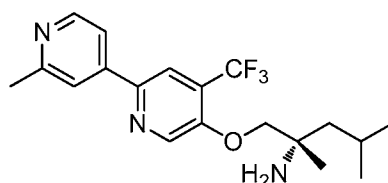
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Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-chloro-5-fluoro-pyridin-4-yl)boronic acid to afford (S)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (9.6 mg, 11%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.61 (d, *J* = 2.6 Hz, 1H), 8.05 (s, 1H), 8.02 (d, *J* = 5.5 Hz, 1H), 7.37 (t, *J* = 53.9 Hz, 1H), 4.04 (s, 2H), 1.81 (dt, *J* = 12.6, 6.4 Hz, 1H), 1.46 - 1.35 (m, 2H), 1.14 (s, 3H), 0.93 (dd, *J* = 12.8, 6.6 Hz, 6H); LCMS (ESI) *m/e* 371.1 [(M-NH₂)⁺, calcd C₁₈H₁₉ClF₃N₂O, 371.1]; LC/MS retention time (method B): *t*_R = 1.97 min.

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Example 144

(S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine



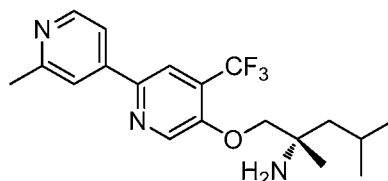
15

Part A: (S)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a 20 mL pressure vial was added (S)-2-amino-2,4-dimethylpentan-1-ol (323 mg, 2.462 mmol) and 2-bromo-5-fluoro-4-(trifluoromethyl)pyridine (601 mg, 2.462 mmol) in tetrahydrofuran (3.3 mL) to give a tan solution. Potassium *tert*-butoxide (2.95 mL, 2.95 mmol) (1.0 M in THF) was added dropwise under nitrogen. After 5 min stirring at rt, the vial was sealed and the mixture was stirred at 80 °C for 18 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried and concentrated to a tan oil. The crude was purified by silica gel chromatography up to 10% MeOH/CH₂Cl₂ to afford (S)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (0.42 g, 48%) as a tan oil: ¹H NMR (400 MHz, Chloroform-d) δ 8.19 (s, 1H), 7.64 (s, 1H),

3.95 - 3.86 (m, 2H), 1.80 (dt, $J = 12.8, 6.4$ Hz, 1H), 1.65 (s, 2H), 1.50 (dd, $J = 5.7, 4.0$ Hz, 2H), 1.25 (s, 3H), 0.99 (dd, $J = 9.1, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, Chloroform- d) δ -64.37; LCMS (ESI) m/e 338.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{13}\text{H}_{16}\text{BrF}_3\text{NO}$, 338.1; LC/MS retention time (method B): $t_R = 1.88$ min.

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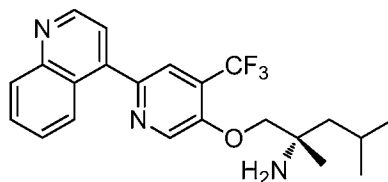
Part B: (S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine

Prepared as described in Example 117 to afford (S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine (25.2 mg, 0.066 mmol, 61% yield): ^1H NMR (500 MHz, DMSO- d_6) δ 8.79 (s, 1H), 8.55 (d, $J = 5.2$ Hz, 1H), 8.28 (s, 1H), 7.96 (s, 1H), 7.87 (d, $J = 5.4$ Hz, 1H), 4.05 (d, $J = 5.5$ Hz, 2H), 2.56 (s, 3H), 1.81 (dt, $J = 12.6, 6.3$ Hz, 1H), 1.45 - 1.33 (m, 2H), 1.12 (s, 3H), 0.92 (dd, $J = 6.6, 3.0$ Hz, 6H); LCMS (ESI) m/e 368.2 $(\text{M}+\text{H})^+$, calcd $\text{C}_{19}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 368.2; LC/MS retention time (method B): $t_R = 1.48$ min.

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Example 145

(S)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine



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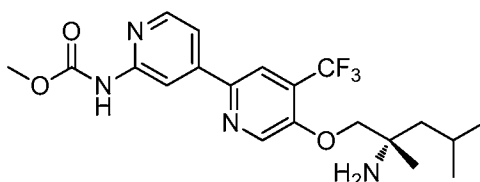
Prepared as described in Example 117 to afford (S)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine (16.2 mg, 0.038 mmol, 58% yield): ^1H NMR (500 MHz, DMSO- d_6) δ 9.01 (d, $J = 4.6$ Hz, 1H), 8.92 (s, 1H), 8.17 (d, $J = 8.3$ Hz, 1H), 8.13 (d, $J = 8.5$ Hz, 1H), 8.03 (s, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 4.4$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 4.20 (d, $J = 3.9$ Hz, 2H), 1.84 (d, $J = 10.3$ Hz, 1H), 1.50 (qd, $J = 14.1, 5.5$ Hz, 2H), 1.23 (s, 3H), 0.95 (t,

25

$J = 6.1$ Hz, 6H); LCMS (ESI) m/e 404.2 ($M+H$)⁺, calcd C₂₂H₂₅F₃N₃O, 404.2];
LC/MS retention time (method B): $t_R = 1.71$ min.

Example 146

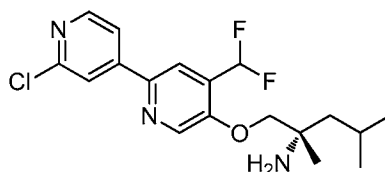
5 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



Prepared as described in Example 117 to afford (S)-methyl (5-((2-amino-2,4-
10 dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (4.4 mg, 0.010 mmol, 18% yield): ¹H NMR (500 MHz, DMSO-d₆) δ 10.31 (s, 1H), 8.82 (s, 1H), 8.55 (s, 1H), 8.37 (d, $J = 5.5$ Hz, 1H), 8.18 (s, 1H), 7.74 (d, $J = 5.4$ Hz, 1H), 4.12 - 3.99 (m, 2H), 3.71 (s, 3H – under solvent peak), 1.81 (dt, $J = 13.2, 6.6$ Hz, 1H), 1.39 (d, $J = 5.6$ Hz, 2H), 1.12 (s, 3H), 0.92 (dd, $J = 6.6, 2.9$ Hz, 6H); LCMS (ESI) m/e 449.2 ($M+Na$)⁺, calcd C₂₀H₂₅F₃N₄NaO₃, 449.2]; LC/MS retention time
15 (method B): $t_R = 1.79$ min.

Example 147

20 (S)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

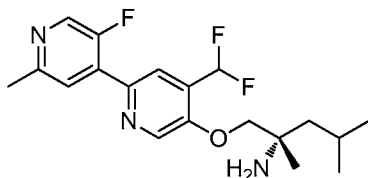


Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-chloro-pyridin-4-yl)boronic acid to afford (S)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine
25 (13.5 mg, 53%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.69 (s, 1H), 8.51 (d, $J = 5.2$ Hz, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 8.09 (d, $J = 5.3$ Hz, 1H), 7.33 (t, $J = 53.8$ Hz, 1H), 4.03 (s, 2H), 1.80 (p, $J = 6.2$ Hz, 1H), 1.41 (qd, $J = 14.0, 5.5$ Hz, 2H), 1.14 (s, 3H),

0.92 (dd, $J = 13.2, 6.6$ Hz, 6H); LCMS (ESI) m/e 370.1 $[(M+H)^+]$, calcd $C_{18}H_{23}ClF_2N_3O$, 370.1]; LC/MS retention time (method B): $t_R = 1.91$ min.

Example 148

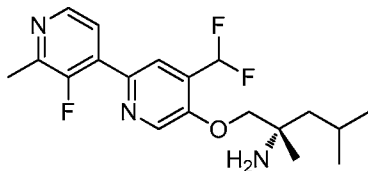
5 (S)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



To a 2 mL vial was added (S)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Example 143) (7.42 mg, 0.019 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (2.402 mg, 0.019 mmol), and Cs₂CO₃ (9.35 mg, 0.029 mmol) in dioxane (0.2 mL) and water (0.1 mL) to give a colorless suspension under nitrogen (degassed for 5 min). 1,1'-Bis(diphenylphosphino)ferrocenepalladium(II) dichloride, toluene (0.787 mg, 0.957 μmol) was added under nitrogen. The vial was sealed and heated at 100 °C for 20 h. The mixture was dried, and diluted with MeOH, filtered and purified by prep-HPLC to afford (S)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (1.8 mg, 26%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.73 (s, 1H), 8.54 (d, $J = 2.9$ Hz, 1H), 7.99 (s, 1H), 7.80 (d, $J = 6.5$ Hz, 1H), 7.38 (t, $J = 53.9$ Hz, 1H), 4.12 - 4.02 (m, 2H), 2.54 (s, 3H), 1.79 (dq, $J = 12.6, 6.2$ Hz, 1H), 1.44 (qd, $J = 14.0, 5.6$ Hz, 2H), 1.17 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H); LCMS (ESI) m/e 351.1 $[(M-NH_2)^+]$, calcd $C_{19}H_{22}F_3N_2O$, 351.2]; LC/MS retention time (method B): $t_R = 1.81$ min.

Example 149

25 (S)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

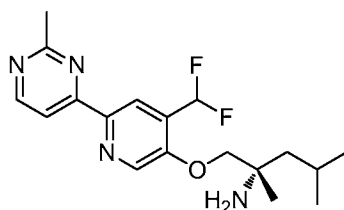


Prepared as previously described in Example 148 with Example 142 as the starting material to afford (*S*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (2.0 mg, 25%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.74 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.01 (s, 1H), 7.77 (t, *J* = 5.5 Hz, 1H), 7.38 (t, *J* = 53.9 Hz, 1H), 4.06 (d, *J* = 3.0 Hz, 2H), 2.54 (d, *J* = 3.4 Hz, 3H), 1.86 - 1.76 (m, 1H), 1.50 - 1.37 (m, 2H), 1.17 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 351.1 [(M-NH₂)⁺, calcd C₁₉H₂₂F₃N₂O, 351.2]; LC/MS retention time (method B): *t*_R = 1.78 min.

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Example 150

(*S*)-1-((4-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

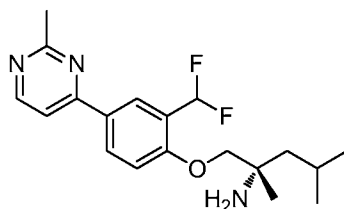


Prepared as previously described in Example 132 to afford (*S*)-1-((4-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (0.8 mg, 2.3% for 2 steps) as a colorless solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.83 (d, *J* = 5.2 Hz, 1H), 8.71 (s, 1H), 8.53 (s, 1H), 8.10 (d, *J* = 5.2 Hz, 1H), 7.41 (s, 1H), 4.08 (d, *J* = 2.2 Hz, 2H), 2.72 (s, 3H), 1.81 (dt, *J* = 12.9, 6.5 Hz, 1H), 1.44 (qd, *J* = 14.0, 5.5 Hz, 2H), 1.17 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 334.1 [(M-NH₂)⁺, calcd C₁₈H₂₂F₂N₃O, 334.2]; LC/MS retention time (method B): *t*_R = 1.83 min.

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Example 152

(*S*)-1-(2-(difluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

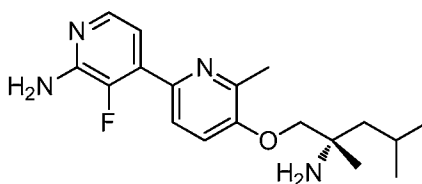


Prepared as previously described in Example 116 with 4-bromo-2-methylpyrimidine to afford (*S*)-1-(2-(difluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (32.2 mg, 56% for 2 steps) as a colorless solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.72 (d, *J* = 5.4 Hz, 1H), 8.38 (d, *J* = 2.2 Hz, 1H), 8.35 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.89 (d, *J* = 5.4 Hz, 1H), 7.43 - 7.16 (m, 2H), 3.87 (s, 2H), 2.68 (s, 3H), 1.80 (dp, *J* = 12.8, 6.3 Hz, 1H), 1.48 - 1.35 (m, 2H), 1.14 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 333.2 [(M-NH₂)⁺, calcd C₁₉H₂₃F₂N₂O, 333.2]; LC/MS retention time (method B): *t*_R = 1.85 min.

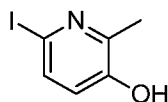
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Example 153

(*S*)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine



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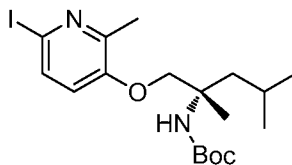


Part A: 6-iodo-2-methylpyridin-3-ol

To a 500 mL round-bottomed flask was added 2-methylpyridin-3-ol (4.0 g, 36.7 mmol) and Na₂CO₃ (7.8 g, 73.6 mmol) in water (100 mL) to give a slightly tan solution/suspension. I₂ (9.6 g, 37.8 mmol) was added in one portion. The mixture was stirred at rt for 3 h. There were noticeable I₂ left. The mixture was stirred overnight and there was still I₂ left. The reaction mixture was heated at 42 °C (bath temp) for 5 h (most I₂ disappeared). The reaction was slowly neutralized with 1N HCl (150 mL) to pH~5. Precipitate was collected by filtration, rinsed with water, aqueous sodium bisulfite solution, and dried under vacuum to yield a yellowish gray powder (7 g). The solids were purified by silica gel chromatography up to 30% EtOAc/hexane to afford 6-iodo-2-methylpyridin-3-ol (4.58 g, 53%) as a light yellow solid: ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.81 (d, *J*

25

= 8.3 Hz, 1H), 2.48 (s, 3H); LCMS (ESI) m/e 235.8 [(M+H)⁺, calcd C₆H₇INO, 236.0]; LC/MS retention time (method B): t_R = 1.14 min.

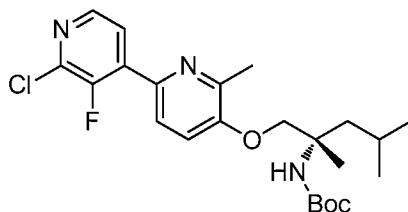


5

Part B: (S)-tert-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as previously described in Example 32 to afford (S)-tert-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (528 mg, 100%) as a tan oil: ¹H NMR (400 MHz, Chloroform-d) δ 7.46 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 4.53 (s, 1H), 4.14 (d, J = 8.9 Hz, 1H), 3.96 (d, J = 8.9 Hz, 1H), 2.46 (s, 3H), 1.83 (tdt, J = 13.2, 11.6, 6.5 Hz, 2H), 1.53 (d, J = 4.7 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 3H), 1.00 (d, J = 3.0 Hz, 3H), 0.98 (d, J = 3.0 Hz, 3H); LCMS (ESI) m/e 448.9 [(M+H)⁺, calcd C₁₈H₃₀IN₂O₃, 449.1]; LC/MS retention time (method B): t_R = 2.38 min.

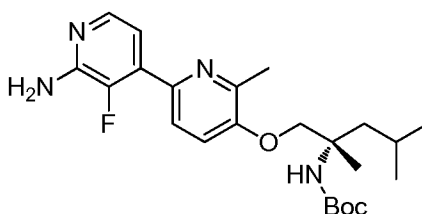
15



Part C: (S)-tert-butyl (1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

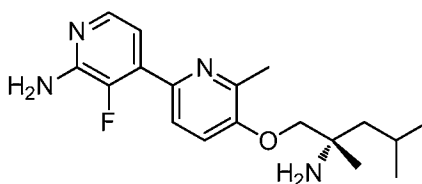
Prepared as previously described in Example 66 to afford (S)-tert-butyl (1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (18.9 mg, 17%): LCMS (ESI) m/e 452.2 [(M+H)⁺, calcd C₂₃H₃₂ClFN₃O₃, 452.2]; LC/MS retention time (method B): t_R = 2.46 min.

20



Part D: (S)-tert-butyl (1-((2'-amino-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

To a 20 mL pressure vial was added (S)-tert-butyl (1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (18.9 mg, 0.042 mmol), and methyl carbamate (4.39 mg, 0.059 mmol) in 1,4-dioxane (0.4 mL) to give a colorless solution. While degassing, PdOAc₂ (0.939 mg, 4.18 μmol), XANTPHOS (4.84 mg, 8.36 μmol), Cs₂CO₃ (20.44 mg, 0.063 mmol) were added. The vial was sealed under nitrogen and heated at 90 °C for 20 h. LCMS showed partial conversion but the carbamate was completely hydrolyzed. The mixture was diluted with EtOAc, dried, filtered, and concentrated. The residue (containing a mixture of the starting material chloride and the hydrolyzed amine product) was directly used in the next step. The amine: LCMS (ESI) *m/e* 433.3 (M+H)⁺, calcd C₂₃H₃₄FN₄O₃, 433.3; LC/MS retention time (method B): *t_R* = 1.99 min; The chloride: LCMS (ESI) *m/e* 452.1 [(M+H)⁺, calcd C₂₃H₃₂ClFN₃O₃, 452.2]; LC/MS retention time (method B): *t_R* = 2.48 min.



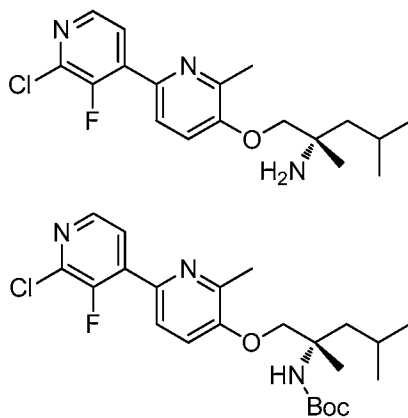
Part E: (S)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine

Prepared as previously described in Example 7, Part B to afford a mixture of the amine and chloride. The mixture was purified by prep-HPLC to afford (S)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine (4.3 mg, 31% for 2 steps): ¹H NMR (500 MHz, DMSO-d₆) δ 7.79 (d, *J* = 5.3 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.02 (t, *J* = 5.2 Hz, 1H), 6.22 (s, 2H), 3.86 (s, 2H), 2.50 (s, 3H), 1.81 (dq, *J* = 12.8, 6.5 Hz, 1H), 1.56 - 1.42 (m, 2H), 1.21 (s,

3H), 0.94 (dd, $J = 10.3, 6.7$ Hz, 6H); LCMS (ESI) m/e 333.2 [(M+H)⁺, calcd C₁₈H₂₆FN₄O, 333.2]; LC/MS retention time (method B): $t_R = 1.48$ min.

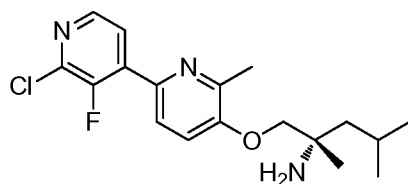
Example 154

- 5 (S)-1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



- 10 *Part A: (S)-tert-butyl (1-((2'-amino-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Obtained as a mixture with the amine from Example 153, Part D. LCMS (ESI) m/e 452.1 [(M+H)⁺, calcd C₂₃H₃₂ClFN₃O₃, 452.2]; LC/MS retention time (method B): $t_R = 2.48$ min.



- 15 *Part B: (S)-1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine*

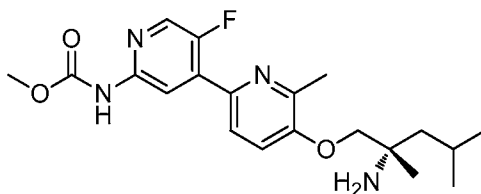
The crude mixture from Example 153, Part D was deprotected as previously described in Example 7, Part B to afford a mixture of the amine and chloride. The mixture was separated and purified by prep-HPLC to afford (S)-1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine: (2.6 mg, 17% for 2 steps): ¹H NMR (500 MHz, DMSO-d₆) δ 8.33 (d, $J = 5.0$ Hz, 1H), 7.99 (t, $J = 5.3$ Hz, 1H), 7.82 (d, $J = 8.3$ Hz, 1H), 7.49 (d, $J = 8.6$ Hz, 1H), 3.83 (s, 2H), 2.51 (s, 3H – OCH₃ protons under DMSO peak – predicted shift = 2.47 ppm), 1.82 (p, $J =$

6.2 Hz, 1H), 1.53 - 1.38 (m, 2H), 1.18 (s, 3H), 0.94 (t, $J = 7.2$ Hz, 6H); LCMS (ESI) m/e 335.1 $[(M-NH_2)^+]$, calcd $C_{18}H_{21}ClFN_2O$, 335.1]; LC/MS retention time (method B): $t_R = 1.91$ min.

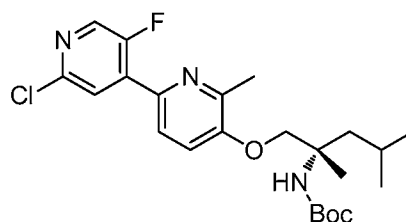
5

Example 155

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

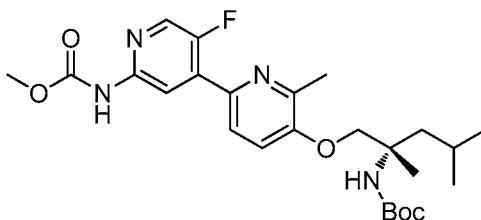


10



Part A: (S)-tert-butyl (1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

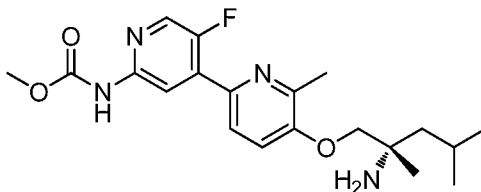
Prepared as previously described in Example 66 with intermediate from
 15 Example 153 and (2-chloro-5-fluoro-pyridin-4-yl)boronic acid to afford (*S*)-tert-butyl (1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (13.4 mg, 13%): LCMS (ESI) m/e 452.1 $[(M+H)^+]$, calcd $C_{23}H_{32}ClFN_3O_3$, 452.2]; LC/MS retention time (method B): $t_R = 2.49$ min.



20

Part B: (*S*)-methyl (5-((2-Boc-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described in Example 153 to afford (*S*)-methyl (5-((2-Boc-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate (no carbamate hydrolysis observed) contaminated with left over starting material ((*S*)-*tert*-butyl (1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate). The crude mixture was carried on without further purification. Carbamate: LCMS (ESI) m/e 491.2 ($M+H$)⁺, calcd C₂₅H₃₆FN₄O₅, 491.3]; LC/MS retention time (method B): t_R = 2.30 min.

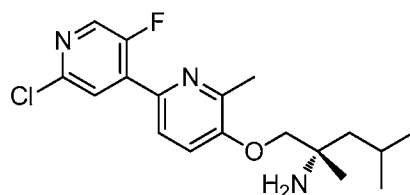


Part C: (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

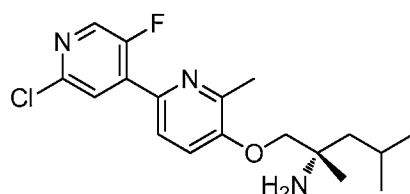
Prepared as previously described in Example 7, Part B. The crude mixture was separated and purified by prep-HPLC to afford (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate (0.3 mg, 2.5% for 2 steps) as a colorless solid. ¹H NMR (400 MHz, Methanol-d₄) δ 8.45 (d, J = 5.9 Hz, 1H), 8.21 (d, J = 2.7 Hz, 1H), 7.79 - 7.73 (m, 1H), 7.46 (d, J = 8.6 Hz, 1H), 4.07 - 3.96 (m, 2H), 3.80 (s, 3H), 2.61 (s, 3H), 1.87 (dt, J = 12.5, 6.4 Hz, 1H), 1.73 (dd, J = 14.3, 5.6 Hz, 1H), 1.62 (dd, J = 14.2, 5.5 Hz, 1H), 1.39 (s, 3H), 1.04 (dd, J = 10.9, 6.6 Hz, 6H); LCMS (ESI) m/e 391.4 [$M+H$]⁺, calcd C₂₀H₂₈FN₄O₃, 391.2].

Example 156

(*S*)-1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



5



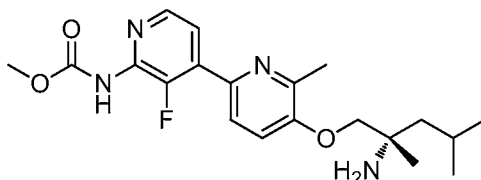
Part C: (*S*)-1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

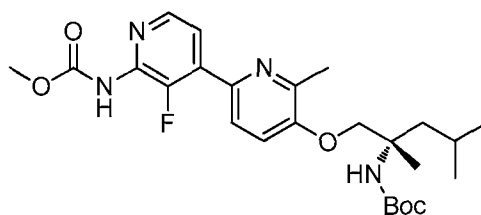
10 Recovered from mixture obtained in Example 155, Part C. The mixture was separated and purified by prep-HPLC to afford (*S*)-1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (5.2 mg, 49% for 2 steps) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 8.54 (d, *J* = 2.6 Hz, 1H), 8.03 (d, *J* = 5.5 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 3.81 (s, 2H), 2.51
 15 (s, 3H – OCH₃ protons under DMSO peak – predicted shift = 2.47 ppm), 1.81 (dq, *J* = 12.6, 6.5 Hz, 1H), 1.49 - 1.36 (m, 2H), 1.16 (s, 3H), 0.93 (t, *J* = 6.3 Hz, 6H); LCMS (ESI) *m/e* 335.1 [(M-NH₂)⁺, calcd C₁₈H₂₁ClFN₂O, 335.1]; LC/MS retention time (method B): *t*_R = 1.93 min.

20

Example 157

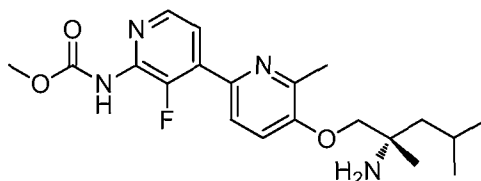
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate





Part A: (S)-methyl (5-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described in Example 153 with reaction running at 80
 5 °C for 30 h resulting in the carbamate after prep-HPLC purification (7.1 mg, 19%):
 LCMS (ESI) m/e 491.4 (M+H)⁺, calcd C₂₅H₃₆FN₄O₅, 491.3]; LC/MS retention time
 (method A): t_R = 1.99 min.



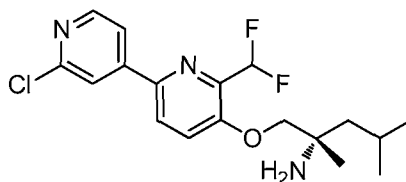
10 *Part B: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate*

Prepared as previously described in Example 7, Part B to afford (S)-methyl
 (5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-
 yl)carbamate (5.2 mg, 90%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.25 (d, J = 5.1 Hz,
 15 1H), 7.79 (t, J = 5.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 8.7 Hz, 1H), 3.80
 (s, 2H), 3.68 (s, 3H), 2.50 (s, 3H), 1.81 (dt, J = 12.5, 6.5 Hz, 1H), 1.48 - 1.38 (m,
 2H), 1.15 (s, 3H), 0.93 (t, J = 6.3 Hz, 6H); LCMS (ESI) m/e 413.1 [(M+Na)⁺, calcd
 C₂₀H₂₇FN₄NaO₃, 413.2]; LC/MS retention time (method B): t_R = 1.66 min.

20

Example 158

(S)-1-((2'-chloro-6-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-
 amine

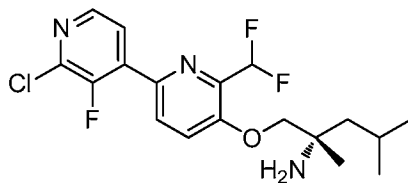


Prepared as described in Example 117 with (2-chloropyridin-4-yl)boronic acid to afford (*S*)-1-((2'-chloro-6-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (26.3 mg, 0.068 mmol, 49%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.52 (d, *J* = 5.2 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.13 (s, 1H), 8.07 (d, *J* = 5.2 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.27 (t, *J* = 53.6 Hz, 1H), 3.94 (s, 2H), 1.79 (dt, *J* = 12.6, 6.4 Hz, 1H), 1.43 (qd, *J* = 14.1, 5.6 Hz, 2H), 1.16 (s, 3H), 0.92 (dd, *J* = 12.8, 6.6 Hz, 6H); LCMS (ESI) *m/e* 370.1 [(M+H)⁺, calcd C₁₉H₂₆F₂N₃O, 370.1]; LC/MS retention time (method B): *t*_R = 1.91 min.

10

Example 159

(*S*)-1-((2'-chloro-6-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



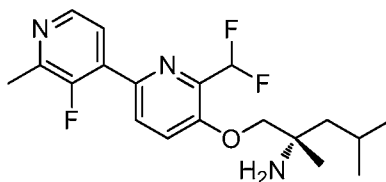
15

Prepared as described in Example 117 with (2-chloro-3-fluoropyridin-4-yl)boronic acid to afford (*S*)-1-((2'-chloro-6-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (25 mg, 0.064 mmol, 9.6%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.38 (dd, *J* = 5.3, 2.4 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 1H), 7.96 (td, *J* = 5.3, 2.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.25 (t, *J* = 53.5 Hz, 1H), 3.91 (d, *J* = 2.0 Hz, 2H), 1.86 - 1.75 (m, 1H), 1.40 (t, *J* = 6.2 Hz, 2H), 1.14 (d, *J* = 2.2 Hz, 3H), 0.92 (ddd, *J* = 9.7, 6.8, 2.3 Hz, 6H); LCMS (ESI) *m/e* 388.1 [(M+H)⁺, calcd C₁₈H₂₂ClF₃N₃O, 388.1]; LC/MS retention time (method B): *t*_R = 1.94 min.

20

Example 160

(*S*)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



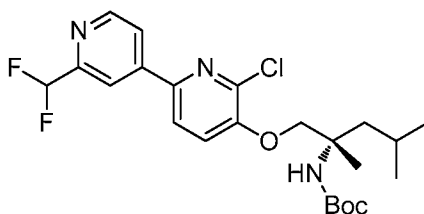
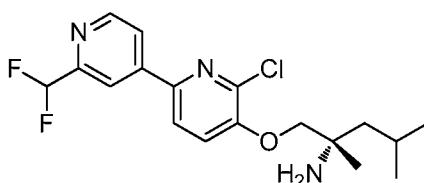
25

Prepared as described in Example 148 to afford (*S*)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (12.8 mg, 0.033 mmol, 55%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.75 (t, *J* = 5.5 Hz, 1H), 7.24 (t, *J* = 53.5 Hz, 1H), 3.92 (s, 2H), 2.54 (d, *J* = 3.3 Hz, 3H), 1.80 (dt, *J* = 12.6, 6.3 Hz, 1H), 1.50 - 1.36 (m, 2H), 1.15 (s, 3H), 0.92 (dd, *J* = 11.5, 6.6 Hz, 6H); LCMS (ESI) *m/e* 368.2 [(*M*+*H*)⁺, calcd C₁₉H₂₅F₃N₃O, 368.2]; LC/MS retention time (method B): *t*_R = 1.72 min.

10

Example 161

((*S*)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

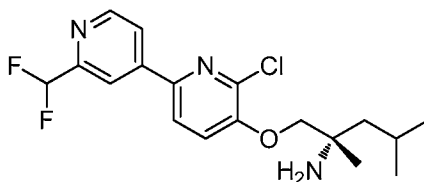


15

Part A: (S)-tert-butyl (1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as previously described in Example 66 with intermediates iodide as described in Example 66 and (2-(difluoromethyl)pyridin-4-yl)boronic acid as described in Example 123 (concentrated to dryness and used as is) to afford (*S*)-*tert*-butyl (1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (70 mg, 19%): ¹H NMR (400 MHz, Chloroform-*d*) δ 8.74 (d, *J* = 5.2 Hz, 1H), 8.18 (d, *J* = 1.7 Hz, 1H), 8.04 - 7.97 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 6.73 (t, *J* = 55.5 Hz, 1H), 4.59 (s, 1H), 4.38 (d, *J* = 8.9 Hz, 1H), 4.18 (d, *J* = 8.8 Hz, 1H), 1.99 - 1.81 (m, 2H), 1.57 - 1.52 (m, 1H), 1.46 (s, 3H), 1.40 (s, 9H), 1.03 (d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (376 MHz,

Chloroform-d) δ -115.83; LCMS (ESI) m/e 470.2 (M+H)⁺, calcd C₂₃H₃₁ClF₂N₃O₃, 470.2]; LC/MS retention time (method A): t_R = 2.50 min.



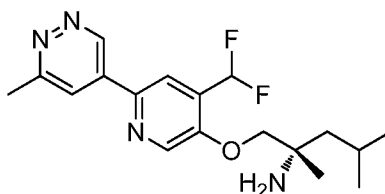
5 *Part B: ((S)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine*

Prepared as previously described in Example 7, Part B to afford ((S)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (40.6 mg, 74%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.77 (d, J = 5.1 Hz, 1H), 8.22 (d, J = 8.1 Hz, 2H), 8.13 (d, J = 5.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 55.0 Hz, 1H), 3.92 (s, 2H), 1.79 (dt, J = 12.5, 6.6 Hz, 1H), 1.44 (qd, J = 14.1, 5.5 Hz, 2H), 1.16 (s, 3H), 0.91 (t, J = 6.2 Hz, 6H); ¹⁹F NMR (376 MHz, DMSO-d₆) δ -115.46 (d, J = 55.0 Hz); LCMS (ESI) m/e 392.1 [(M+Na)⁺, calcd C₁₈H₂₂ClF₂N₃NaO, 392.1]; LC/MS retention time (method B): t_R = 1.94 min.

15

Example 162

(S)-1-((4-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

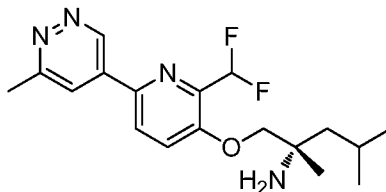


20 Prepared as described in Example 117 with 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine to afford (S)-1-((4-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (23.6 mg, 0.066 mmol, 48%): ¹H NMR (500 MHz, DMSO-d₆) δ 9.72 (d, J = 2.1 Hz, 1H), 8.72 (s, 1H), 8.34 (s, 1H), 8.19 (d, J = 2.0 Hz, 1H), 7.35 (t, J = 54.0 Hz, 1H), 4.04 (s, 2H), 2.71 (s, 3H), 1.85 - 1.74 (m, 1H), 1.42 (qd, J = 13.7, 5.3 Hz, 2H), 1.15 (s, 3H), 0.92 (dd, J = 13.3, 6.7 Hz, 6H); LCMS (ESI) m/e 373.2 [(M+Na)⁺, calcd C₁₈H₂₄F₂N₄NaO, 373.2]; LC/MS retention time (method B): t_R = 1.59 min.

25

Example 163

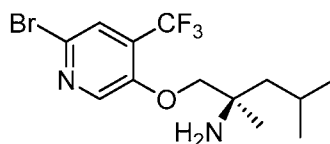
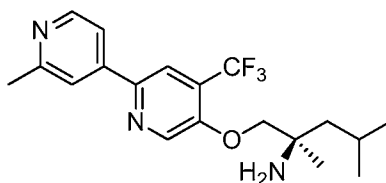
(*S*)-1-((2-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



- 5 Prepared as described in Example 117 with 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine to afford (*S*)-1-((2-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (37.2 mg, 0.105 mmol, 85%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.71 (d, *J* = 2.1 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.24 (t, *J* = 53.6 Hz, 1H), 3.91 (s, 2H), 2.71 (s, 3H), 1.80 (dt, *J* = 13.2, 6.3 Hz, 1H), 1.46 - 1.34 (m, 2H), 1.13 (s, 3H), 0.92 (dd, *J* = 10.5, 6.6 Hz, 6H); LCMS (ESI) *m/e* 373.2 [(*M*+Na)⁺, calcd C₁₈H₂₄F₂N₄NaO, 373.2]; LC/MS retention time (method B): *t*_R = 1.62 min.

Example 164

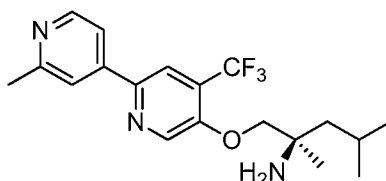
- 15 (*R*)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine



- 20 *Part A: (R)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine*

- Prepared as previously described in Example 144 with *R*-enantiomer of the amino alcohol to afford (*R*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (0.58 g, 97%) as a tan oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 7.64 (s, 1H), 3.97 - 3.83 (m, 2H), 1.85 - 1.73 (m, 1H), 1.49 (dd, *J* =

5.7, 4.0 Hz, 2H), 1.24 (s, 3H), 0.99 (dd, $J = 9.3, 6.6$ Hz, 6H); ^{19}F NMR (376 MHz, Chloroform- d) δ -64.39; LCMS (ESI) m/e 338.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{13}\text{H}_{16}\text{BrF}_3\text{NO}$, 338.1]; LC/MS retention time (method B): $t_R = 1.87$ min.

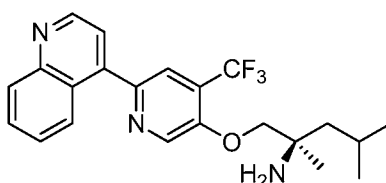


Part B: (R)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine

Prepared as described in Example 144 to afford (R)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine (7.6 mg, 0.020 mmol, 23% yield): ^1H NMR (500 MHz, DMSO- d_6) δ 8.79 (s, 1H), 8.55 (d, $J = 5.2$ Hz, 1H), 8.29 (s, 1H), 7.97 (s, 1H), 7.88 (d, $J = 5.2$ Hz, 1H), 4.11 - 4.02 (m, 2H), 2.56 (s, 3H), 1.81 (dt, $J = 12.9, 6.5$ Hz, 1H), 1.40 (dd, $J = 5.6, 2.8$ Hz, 2H), 1.13 (s, 3H), 0.92 (dd, $J = 6.6, 3.2$ Hz, 6H); LCMS (ESI) m/e 368.2 $(\text{M}+\text{H})^+$, calcd $\text{C}_{19}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 368.2]; LC/MS retention time (method B): $t_R = 1.44$ min.

Example 165

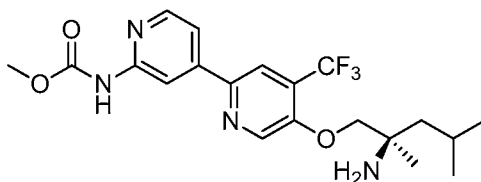
(R)-2,4-dimethyl-1-(((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine



Prepared as described in Example 144 to afford (R)-2,4-dimethyl-1-(((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine (14.9 mg, 0.037 mmol, 45% yield): ^1H NMR (500 MHz, DMSO- d_6) δ 9.01 (d, $J = 4.4$ Hz, 1H), 8.90 (s, 1H), 8.18 (d, $J = 8.5$ Hz, 1H), 8.13 (d, $J = 8.5$ Hz, 1H), 8.02 (s, 1H), 7.82 (t, $J = 7.6$ Hz, 1H), 7.70 (d, $J = 4.4$ Hz, 1H), 7.64 (t, $J = 7.7$ Hz, 1H), 4.15 - 4.05 (m, 2H), 1.83 (dq, $J = 12.6, 6.3$ Hz, 1H), 1.42 (dd, $J = 5.7, 2.0$ Hz, 2H), 1.16 (s, 3H), 0.95 (dd, $J = 6.6, 3.5$ Hz, 6H); LCMS (ESI) m/e 404.2 $(\text{M}+\text{H})^+$, calcd $\text{C}_{22}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 404.2]; LC/MS retention time (method B): $t_R = 1.66$ min.

Example 166

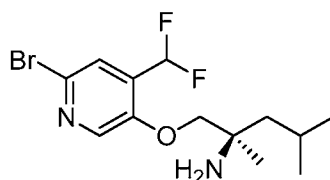
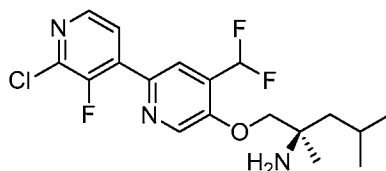
(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



5 Prepared as described in Example 144 to afford (*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (7.8 mg, 0.018 mmol, 35% yield): ¹H NMR (500 MHz, DMSO-d₆) δ 8.81 (s, 1H), 8.54 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.18 (s, 1H), 7.74 (dd, *J* = 5.3, 1.6 Hz, 1H), 4.10 - 4.00 (m, 2H), 3.71 (s, 3H), 1.81 (hept, *J* = 6.1 Hz, 1H), 1.41 - 1.34 (m, 2H), 1.12 (s, 3H),
10 0.92 (dd, *J* = 6.8, 2.7 Hz, 6H); LCMS (ESI) *m/e* 449.1 (M+Na)⁺, calcd C₂₀H₂₅F₃N₄NaO₃, 449.2]; LC/MS retention time (method B): *t*_R = 1.72 min.

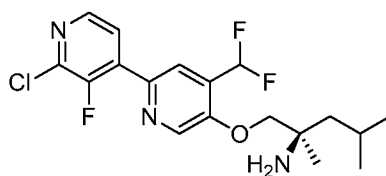
Example 167

(*R*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (*R*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

20 Prepared as previously described in Example 142 with *R*-enantiomer of the amino alcohol to afford (*R*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (740 mg, 95%): LCMS (ESI) *m/e* 336.9 [(M+H)⁺, calcd C₁₃H₂₀BrF₂N₂O, 337.1]; LC/MS retention time (method B): *t*_R = 1.83 min. The
25 material was used as is.

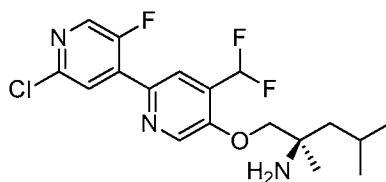


Prepared as previously described in Example 142 with intermediate as described above and (2-chloro-3-fluoro-pyridin-4-yl)boronic acid (6.7 mg, 11%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.38 (d, *J* = 5.0 Hz, 1H), 8.06 (s, 1H), 7.97 (t, *J* = 5.4 Hz, 1H), 7.38 (t, *J* = 53.9 Hz, 1H), 4.05 (s, 2H), 1.81 (dt, *J* = 12.9, 6.4 Hz, 1H), 1.42 (tt, *J* = 14.1, 6.8 Hz, 2H), 1.15 (d, *J* = 3.5 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 371.1 [(M-NH₂)⁺, calcd C₁₈H₁₉ClF₃N₂O, 371.1]; LC/MS retention time (method B): *t*_R = 2.02 min.

10

Example 168

(*R*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

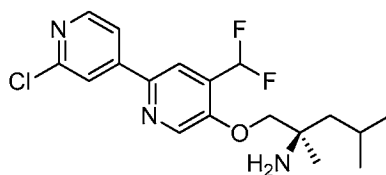


Prepared as previously described in Example 142 with intermediate as described in Example 167 and (2-chloro-5-fluoro-pyridin-4-yl)boronic acid to afford (*R*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (14 mg, 20%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.75 (s, 1H), 8.60 (d, *J* = 2.3 Hz, 1H), 8.05 (s, 1H), 8.02 (d, *J* = 5.5 Hz, 1H), 7.36 (t, *J* = 53.9 Hz, 1H), 4.04 (s, 2H), 1.81 (hept, *J* = 6.4 Hz, 1H), 1.48 - 1.35 (m, 2H), 1.14 (d, *J* = 3.3 Hz, 3H), 0.93 (dd, *J* = 12.6, 6.6 Hz, 6H); LCMS (ESI) *m/e* 371.1 [(M-NH₂)⁺, calcd C₁₈H₁₉ClF₃N₂O, 371.1]; LC/MS retention time (method B): *t*_R = 1.98 min.

20

Example 169

(*R*)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



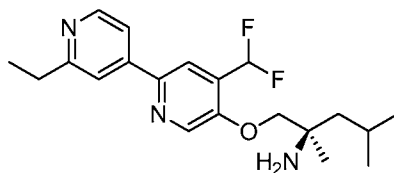
25

Prepared as previously described in Example 142 with intermediate as described in Example 167 and (2-chloro-pyridin-4-yl)boronic acid to afford (*R*)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (10.2 mg, 49%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.70 (s, 1H), 8.51 (d, *J* = 5.3 Hz, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 8.11 (d, *J* = 5.3 Hz, 1H), 7.33 (t, *J* = 53.9 Hz, 1H), 4.02 (s, 2H), 1.80 (q, *J* = 6.3 Hz, 1H), 1.40 (tt, *J* = 14.0, 7.4 Hz, 2H), 1.14 (s, 3H), 0.93 (dd, *J* = 12.5, 6.6 Hz, 6H); LCMS (ESI) *m/e* 353.1 [(*M*-NH₂)⁺, calcd C₁₈H₂₀ClF₂N₂O, 353.1]; LC/MS retention time (method B): *t*_R = 1.90 min.

10

Example 170

(*R*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

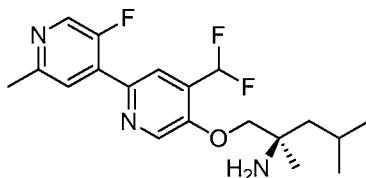


Prepared as previously described in Example 141 with intermediate as described in Example 167 and (2-ethylpyridin-4-yl)boronic acid to afford (*R*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (12.3 mg, 60%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.68 (s, 1H), 8.57 (d, *J* = 5.3 Hz, 1H), 8.20 (s, 1H), 7.94 (s, 1H), 7.88 - 7.84 (m, 1H), 7.35 (t, *J* = 53.9 Hz, 1H), 4.02 (s, 2H), 2.84 (q, *J* = 7.6 Hz, 2H), 1.81 (dt, *J* = 12.7, 6.5 Hz, 1H), 1.42 (qd, *J* = 14.0, 5.5 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.15 (s, 3H), 0.93 (dd, *J* = 13.5, 6.6 Hz, 6H); LCMS (ESI) *m/e* 364.2 [(*M*+H)⁺, calcd C₂₀H₂₈F₂N₃O, 364.2]; LC/MS retention time (method B): *t*_R = 1.48 min.

25

Example 171

(*R*)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

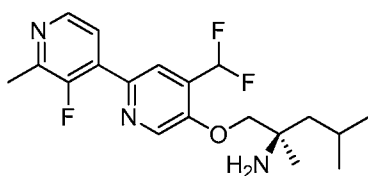


Prepared as previously described in Example 148 with Example 168 to afford (*R*)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (1.2 mg, 10%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.74 (s, 1H), 8.55 (d, *J* = 2.9 Hz, 1H), 7.99 (s, 1H), 7.81 (d, *J* = 6.5 Hz, 1H), 7.40 (t, *J* = 53.8 Hz, 1H), 4.15 - 4.05 (m, 2H), 2.54 (s, 3H), 1.81 (dt, *J* = 12.8, 6.3 Hz, 1H), 1.54 - 1.39 (m, 2H), 1.19 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 351.1 [(M-NH₂)⁺, calcd C₁₉H₂₂F₃N₂O, 351.2]; LC/MS retention time (method B): *t*_R = 1.80 min.

10

Example 172

(*R*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



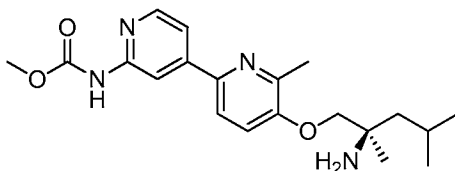
Prepared as previously described in Example 148 with Example 167 as the starting material to afford (*R*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (1.1 mg, 24%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.02 (s, 1H), 7.77 (t, *J* = 5.5 Hz, 1H), 7.43 (t, *J* = 53.9 Hz, 1H), 4.13 (q, *J* = 9.5 Hz, 2H), 2.54 (d, *J* = 3.3 Hz, 3H), 1.81 (dt, *J* = 12.9, 6.4 Hz, 1H), 1.57 - 1.41 (m, 2H), 1.22 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 351.1 [(M-NH₂)⁺, calcd C₁₉H₂₂F₃N₂O, 351.2]; LC/MS retention time (method B): *t*_R = 1.79 min.

20

Example 173

(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

25

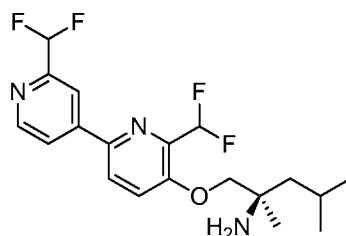


Prepared as previously described in Example 164 using the *R*-enantiomer of the amino alcohol to afford (*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-

methyl-[2,4'-bipyridin]-2'-yl)carbamate (26 mg, 0.050 mmol, 26%) as a pale yellow film. ¹H NMR (400MHz, MeOH-d₄) δ 8.36 (d, *J*=6.5 Hz, 1H), 8.24 (d, *J*=1.3 Hz, 1H), 8.05 (m, 2H), 7.58 (d, *J*=8.5 Hz, 1H), 4.25 (m, 2H), 3.94 (s, 3H), 3.38 (s, 2 H), 2.66 (s, 3H), 1.95-1.85 (m, 2H), 1.81-1.71 (m, 1H), 1.55 (s, 3H), 1.09 (d, *J*=6.5 Hz, 3H), 1.04 (d, *J*=6.4 Hz, 3H); LCMS (ESI) *m/e* 373.4 (M+H)⁺, calcd C₂₀H₂₉N₄O₃, 373.2]; LC/MS retention time (method D): *t_R* = 1.81 min.

Example 174

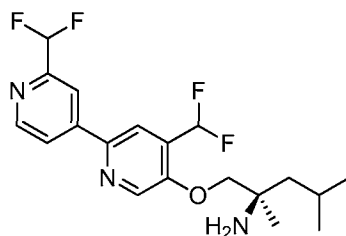
(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 123 using the *R*-enantiomer of the amino alcohol to afford (*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (6.6 mg, 0.017 mmol, 15%) as a film. ¹H NMR (500MHz, DMSO-d₆) δ 8.79 (d, *J*=5.1 Hz, 1H), 8.40 (d, *J*=8.8 Hz, 1H), 8.33 (s, 1H), 8.22 (d, *J*=5.1 Hz, 1H), 7.82 (d, *J*=8.8 Hz, 1H), 7.25 (t, *J*=53.5 Hz, 1H), 7.05 (t, *J*=54.9 Hz, 1H), 3.91 (s, 2H), 3.36 (m 2H), 1.81(m, 1H), 1.40 (m, 2H), 1.13 (s, 3H) 0.94 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.4 Hz, 3H); LCMS (ESI) *m/e* 386.4 (M+H)⁺, calcd C₁₉H₂₄F₄N₃O, 386.2]; LC/MS retention time (method D): *t_R* = 2.62 min.

Example 175

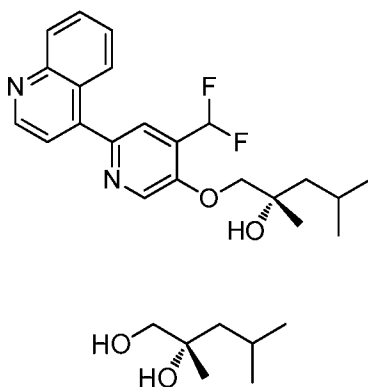
(*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 124 using the *R*-enantiomer of the amino alcohol to afford (*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (9.3 mg, 0.024 mmol, 21%) as a film. ¹H NMR (500MHz, DMSO-d₆) δ 8.79 (d, *J*=5.1 Hz, 1H), 8.71 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.25 (d, *J*=4.8 Hz, 1H), 7.33 (t, *J*=53.5 Hz, 1H), 7.04 (t, *J*=54.9 Hz, 1H), 4.01 (s, 2H), 3.32 (m, 2H), 1.81(m, 1H), 1.40 (m, 2H), 1.13 (s, 3H) 0.94 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.4 Hz, 3H); LCMS (ESI) *m/e* 386.4 (M+H)⁺, calcd C₁₉H₂₄F₄N₃O, 386.2]; LC/MS retention time (method D): *t_R* = 2.66 min.

Example 176

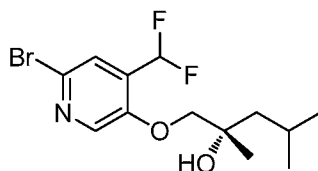
(*S*)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol



Part A: (S)-2,4-dimethylpentane-1,2-diol

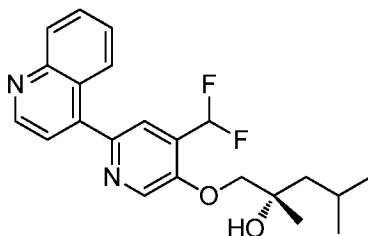
To a 500 mL round-bottomed flask was added AD-MIX-ALPHA (3.60 g, 2.60 mmol) in BuOH (13 mL) and water (13 mL) to give a yellow solution under vigorously stirring. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A precipitate appeared and 2,4-dimethylpent-1-ene (0.364 mL, 2.60 mmol) was added in one portion. The resulting mixture was stirred vigorously at 0 °C for 6 h and 3.86 g (30.6 mmol) of sodium sulfite was added. The mixture was allowed to warm to rt and was stirred for 30 min. CH₂Cl₂ (40 mL) and water (80 mL) was then added successively and the layers were separated. The aqueous layer was extracted twice with CH₂Cl₂. The combined organic phase was dried, filtered, and concentrated to afford (*S*)-2,4-dimethylpentane-1,2-diol (308 mg, 90%) as a colorless oil: ¹H NMR (400 MHz, Chloroform-d) δ 3.52 - 3.38 (m, 2H), 1.85 - 1.79 (m, 1H), 1.42 (dd, *J* = 6.0, 2.0 Hz, 2H), 1.22 (s, 3H), 0.99 (dd, *J* = 11.7, 6.6 Hz, 6H).

Reference: S. J. Leiris *et al. Bioorg. Med. Chem.* **2010**, *18*, 3481-3493.



Part B: (S)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol

5 To a 20 mL pressure bottle was added (*S*)-2,4-dimethylpentane-1,2-diol (125 mg, 0.946 mmol) and 2-bromo-4-(difluoromethyl)-5-fluoropyridine (214 mg, 0.946 mmol) in tetrahydrofuran (1.3 mL) to give a tan solution. Potassium *tert*-butoxide (1.229 mL, 1.229 mmol) (1.0 M in THF) was added dropwise under nitrogen. After 5 min stirring at rt, the bottle was sealed and the mixture was stirred at 80 °C for 18
10 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried and concentrated to afford (*S*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol (300 mg, 94%) as a tan oil. The material was used as is. LCMS (ESI) *m/e* 338.0 [(M+H)⁺, calcd
15 C₁₃H₁₉BrF₂NO₂, 338.0]; LC/MS retention time (method B): *t*_R = 2.30 min.

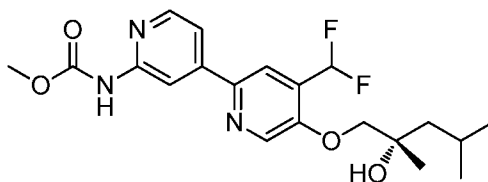


Part C: (S)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol

20 Prepared as previously described in Example 117 to afford (*S*)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol (3.6 mg, 14%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.00 (d, *J* = 4.4 Hz, 1H), 8.80 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.69 - 7.61 (m, 2H), 7.35 (s, 1H), 4.09 (q, *J* = 9.2 Hz, 2H), 1.86 (dt, *J* = 12.7,
25 6.5 Hz, 1H), 1.50 (d, *J* = 5.9 Hz, 2H), 1.27 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 6H); LCMS (ESI) *m/e* 387.1 [(M+H)⁺, calcd C₂₂H₂₅F₂N₂O₂, 387.2]; LC/MS retention time (method B): *t*_R = 2.06 min.

Example 177

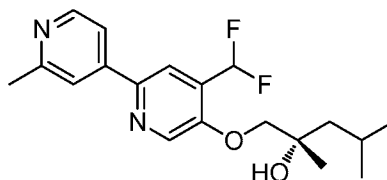
(*S*)-methyl (4-(difluoromethyl)-5-((2-hydroxy-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate



- 5 Prepared as previously described in Example 117 with intermediate from Example 176 (1.8 mg, 6.5%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.71 (s, 1H), 8.53 (s, 1H), 8.36 (d, $J = 5.4$ Hz, 1H), 8.07 (s, 1H), 7.77 - 7.67 (m, 1H), 7.31 (s, 1H), 4.05 (q, $J = 9.3$ Hz, 2H), 3.71 (s, 3H), 1.83 (dt, $J = 12.6, 6.3$ Hz, 1H), 1.47 (d, $J = 5.9$ Hz, 2H), 1.24 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 6H); LCMS (ESI) m/e 410.1 [(M+H) $^+$, calcd $\text{C}_{20}\text{H}_{26}\text{F}_2\text{N}_3\text{O}_4$, 410.2]; LC/MS retention time (method B): $t_R = 2.07$ min.
- 10

Example 178

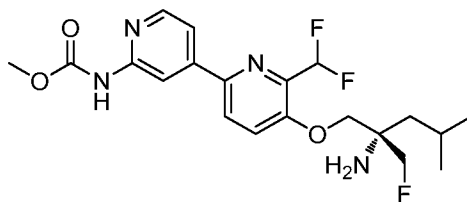
(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-ol



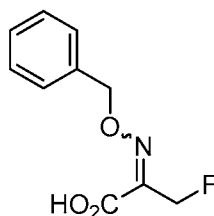
- 15 Prepared as previously described in Example 117 with intermediate from Example 176 to afford (*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-ol (2.2 mg, 7.2%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.54 (d, $J = 5.3$ Hz, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.84 (d, $J = 5.7$ Hz, 1H), 7.30 (t, $J = 54.1$ Hz, 1H), 4.04 (q, $J = 9.2$ Hz, 2H), 2.56 (s, 3H), 1.83 (dt, $J = 12.8, 6.4$ Hz, 1H), 1.46 (d, $J = 5.9$ Hz, 2H), 1.24 (s, 3H), 0.94 (dd, $J = 6.7, 1.6$ Hz, 6H); LCMS (ESI) m/e 351.1 [(M+H) $^+$, calcd $\text{C}_{19}\text{H}_{25}\text{F}_2\text{N}_2\text{O}_2$, 351.2]; LC/MS retention time (method B): $t_R = 1.91$ min.
- 20

Example 179

(*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

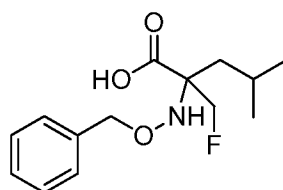


5



Part A: (E/Z)-2-((benzyloxy)imino)-3-fluoropropanoic acid

To a 250 mL round-bottomed flask was added *O*-benzylhydroxylamine (1.5338 g, 12.45 mmol) and sodium 3-fluoro-2-oxopropanoate (1.595 g, 12.45 mmol) in ethanol (36 mL) to give a white suspension. The mixture was heated at 80 °C for 15 h. The ethanol was stripped off. The off-white solid was dissolved in EtOAc and 15 mL 1N HCl. The layer was separated. The aqueous layer was extracted three time with EtOAc. The combined organic solution was dried and concentrated to afford (*E/Z*)-2-((benzyloxy)imino)-3-fluoropropanoic acid (2.51 g, 96%) as a tan solid. LCMS indicated likely *E/Z* isomers (about 1/4 ratio). The material was used as is.



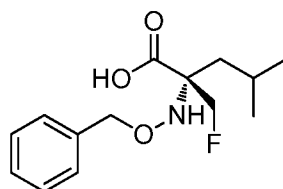
Part B: 2-((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid

To a 250 mL round-bottomed flask was added (*E/Z*)-2-((benzyloxy)imino)-3-fluoropropanoic acid (2.32 g, 10.99 mmol) and 3-bromo-2-methylpropene (4.43 mL, 43.9 mmol) in THF (10.00 mL) and aqueous NH₄Cl (50 mL) to give a tan solution. Zinc (3.59 g, 54.9 mmol) was added portionwise. The mixture was stirred at rt for 30 min. The mixture was diluted with water and EtOAc. The layers were separated.

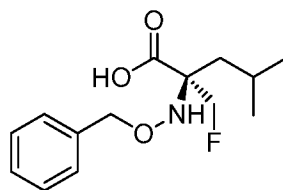
The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried and concentrated to a dense semi-solid. First silica gel chromatography up to 50% EtOAc/hexane did not purify the desired product and the 2nd silica gel chromatography up to 10% MeOH/CH₂Cl₂ (Rf~0.3) afforded 2-
 5 ((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid (2.33 g, 76%) as a white solid: ¹H NMR (400 MHz, Chloroform-d) δ 7.44 - 7.31 (m, 5H), 6.94 (s, 1H), 4.98 (p, *J* = 1.6 Hz, 1H), 4.88 (d, *J* = 2.3 Hz, 1H), 4.87 - 4.61 (m, 4H), 2.40 (d, *J* = 1.2 Hz, 2H), 1.77 (s, 3H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -233.34; LCMS (ESI) *m/e* 290.1 [(M+Na)⁺, calcd C₁₄H₁₈FNNaO₃, 290.1]; LC/MS retention time
 10 (method B): *t_R* = 2.04 min.

The racemic compound (2 g) was separated by chiral super critical fluid chromatography (Column: ChiralPak AD-H, 30 x 250mm, 5μm); Mobile Phase: 10 % EtOH / 90% CO₂ to give the two enantiomers.

Analytical super critical fluid chromatography conditions: Column: ChiralPak
 15 AD-H, 4.6 x 250mm, 5μm; BPR pressure: 100 bars; Temperature: 35 °C; Flow rate: 2.0 mL/min; Mobile Phase: 20 % EtOH / 80% CO₂; Detector Wavelength: UV 205 nm.



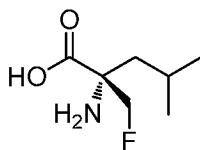
Enantiomer 1 (0.9 g, 90% recovery, e.e.% > 99.9%, α_D = +7.87° (CHCl₃, 3.05
 20 mg/ml)): (*S*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 3.00 min.



Enantiomer 2 (0.9 g, 90% recovery, e.e.% = 92.6%, α_D = -9.20° (CHCl₃, 3.15
 mg/ml)): (*R*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate
 25 2,2-dioxide HPLC retention time = 3.52 min.

The absolute structures were assigned based on the comparison of the optical rotations of the free amino alcohol below with the des-F analogs, and were further

proved by the biology data of the final examples (analogs made from the *S*-enantiomer (1) were more potent than analogs made from the *R*-enantiomer (2) as was seen with the other examples).

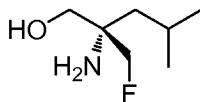


5

Part C: (S)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid

To a 1 L round-bottomed flask was added (*S*)-2-((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid (0.89 g, 3.33 mmol) in MeOH (30 mL) to give a colorless solution. Pd-C (0.709 g, 0.666 mmol) was added. The mixture was stirred under hydrogen (balloon) for 16 h. LCMS showed complete disappearance of starting material. The mixture was filtered and rinsed with MeOH. The filtered clear solution was concentrated to afford (*S*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid (510 mg, 94%) as a white solid: ¹H NMR (400 MHz, Methanol-d₄) δ 4.62 (ddd, *J* = 62.0, 47.4, 10.0 Hz, 2H), 1.94 - 1.66 (m, 3H), 1.01 (dd, *J* = 6.3, 3.9 Hz, 6H); ¹⁹F NMR (376 MHz, Methanol-d₄) δ -229.19; α_D = +21.61° (MeOH, 2.85 mg/mL).

15

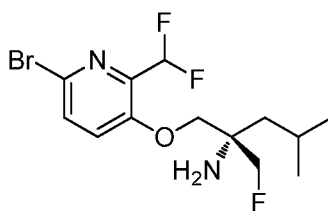


Part D: (S)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol

To a 250 mL round-bottomed flask was added (*S*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid (496 mg, 3.04 mmol) in tetrahydrofuran (15 mL) to give a colorless solution under nitrogen. BH₃.THF (12.16 mL, 12.16 mmol) was added under nitrogen. The mixture was stirred at rt over the weekend for 66 h. TLC showed (10% MeOH/CH₂Cl₂, I₂ stain) a new peak above the baseline. The reaction was quenched with MeOH. Volatiles were removed. The residue was treated with 30 mL 1N HCl and heated at 50 °C for 1 h. After cooling down, the mixture was then basified with 40 mL 1N NaOH and extracted three times with CH₂Cl₂. The combined organic solution was dried and concentrated to give (*S*)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol (377 mg, 83%) as a colorless oil: ¹H NMR (400 MHz, Chloroform-d) δ 4.31 (dd, *J* = 47.7, 0.9 Hz, 2H), 3.53 (dd, *J* = 10.8, 1.3 Hz,

25

1H), 3.42 (dd, $J = 10.8, 3.0$ Hz, 1H), 1.79 (m, 4H), 1.44 - 1.32 (m, 2H), 1.00 (d, $J = 1.8$ Hz, 3H), 0.99 (d, $J = 1.8$ Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -227.90; $\alpha_D = -1.00^\circ$ (CHCl_3 , 2.40 mg/mL).

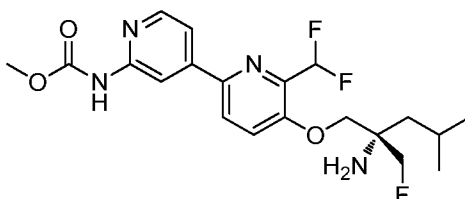


5

Part E: (S)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

To a 2 mL pressure bottle was added (S)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol (65.7 mg, 0.440 mmol) and 6-bromo-2-(difluoromethyl)-3-fluoropyridine (100 mg, 0.440 mmol) in tetrahydrofuran (0.6 mL) to give a colorless solution. Potassium *tert*-butoxide (0.528 mL, 0.528 mmol) (1.0 M in THF) was added under nitrogen. The bottle was sealed and the mixture was stirred at 70 °C for 16 h. The mixture was partitioned between water and EtOAc. The layers were separated. The aqueous layer was extracted with EtOAc. The combined organic solution was washed with brine, dried and concentrated to a tan oil (140 mg, 90%): ^1H NMR (400 MHz, Chloroform- d) δ 7.56 (dt, $J = 8.7, 1.0$ Hz, 1H), 7.26 (d, $J = 8.8$ Hz, 1H), 6.68 (t, $J = 53.8$ Hz, 1H), 4.50 - 4.25 (m, 2H), 3.93 (ddd, $J = 32.5, 8.5, 1.8$ Hz, 2H), 1.87 (dq, $J = 12.7, 6.3$ Hz, 1H), 1.52 - 1.44 (m, 2H), 1.03 (d, $J = 6.7$ Hz, 3H), 1.00 (d, $J = 6.7$ Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -117.34, -225.58; LCMS (ESI) m/e 355.1 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{13}\text{H}_{19}\text{BrF}_3\text{N}_2\text{O}$, 355.1; LC/MS retention time (method B): $t_R = 1.69$ min.

20



Part F: (S)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

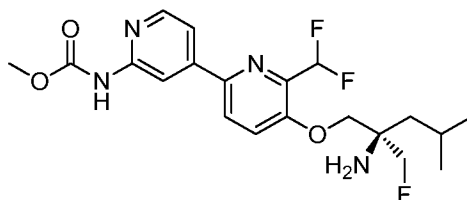
25

Prepared as previously described for Example 117 but at 80 °C for 5 h to afford the titled product (9.7 mg, 36%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.50 (s,

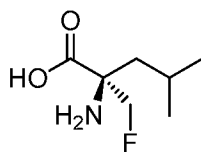
1H), 8.36 (d, $J = 5.2$ Hz, 1H), 8.18 (d, $J = 8.8$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.67 (d, $J = 5.3$ Hz, 1H), 7.23 (t, $J = 53.5$ Hz, 1H), 4.33 (dq, $J = 47.8, 8.9$ Hz, 2H), 4.07 - 3.92 (m, 2H), 3.71 (s, 3H), 1.89 (dd, $J = 12.7, 6.5$ Hz, 1H), 1.50 - 1.31 (m, 2H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H); LCMS (ESI) m/e 427.3 $[(M+H)^+]$, calcd C₂₀H₂₆F₃N₄O₃, 427.2; LC/MS retention time (method B): $t_R = 1.66$ min.

Example 180

(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



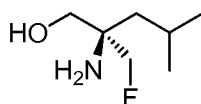
10



Part A: (*R*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid

Prepared as previously described in Example 179, Part C to afford (*R*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid (512 mg, 94%) as a white solid: ¹H NMR (400 MHz, Methanol-d₄) δ 4.62 (ddd, $J = 62.0, 47.4, 10.0$ Hz, 2H), 1.94 - 1.66 (m, 3H), 1.01 (dd, $J = 6.3, 3.9$ Hz, 6H); ¹⁹F NMR (376 MHz, Methanol-d₄) δ -229.19; $\alpha_D = -20.29^\circ$ (MeOH, 2.70 mg/mL).

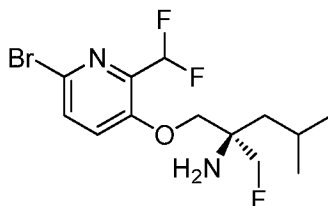
20



Part B: (*R*)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol

Prepared as previously described in Example 179, Part D to afford (*R*)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol (362 mg, 80%) as a colorless oil: ¹H NMR (400 MHz, Methanol-d₄) δ 4.31 (d, $J = 47.7$ Hz, 2H), 3.53 (dd, $J = 10.8, 1.3$ Hz, 1H), 3.42 (dd, $J = 10.8, 3.0$ Hz, 1H), 1.79 (tt, $J = 12.8, 6.4$ Hz, 4H), 1.38 (td, $J =$

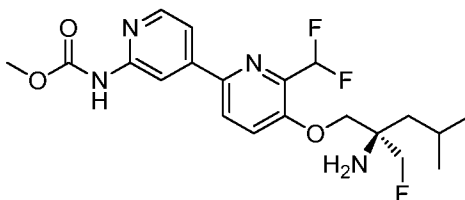
5.6, 1.8 Hz, 2H), 1.00 (d, $J = 1.8$ Hz, 3H), 0.99 (d, $J = 1.9$ Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -227.87; $\alpha_D = +1.11^\circ$ (CHCl_3 , 2.70 mg/mL).



5 *Part C: (R)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine*

Prepared as previously described in Example 179, Part E to afford (R)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (145 mg, 96%) as a colorless oil: ^1H NMR (400 MHz, Methanol- d_4) δ 7.56 (dt, $J = 8.6, 1.0$ Hz, 1H), 7.26 (d, $J = 8.7$ Hz, 1H), 6.69 (t, $J = 53.8$ Hz, 1H), 4.49 - 4.26 (m, 2H), 3.93 (ddd, $J = 32.8, 8.6, 1.8$ Hz, 2H), 1.88 (dp, $J = 12.8, 6.4$ Hz, 1H), 1.56 - 1.41 (m, 4H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.00 (d, $J = 6.6$ Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -117.50, -225.55; LCMS (ESI) m/e 355.1 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{13}\text{H}_{19}\text{BrF}_3\text{N}_2\text{O}$, 355.1]; LC/MS retention time (method B): $t_R = 1.68$ min.

15



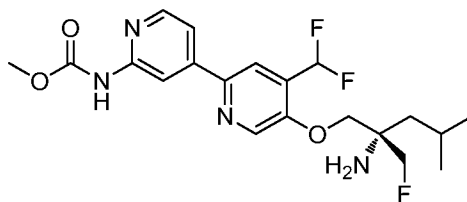
Part D: (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described In Example 179 to afford (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (8.8 mg, 33%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.50 (s, 1H), 8.36 (d, $J = 5.4$ Hz, 1H), 8.18 (d, $J = 8.7$ Hz, 1H), 7.83 (d, $J = 8.8$ Hz, 1H), 7.67 (d, $J = 5.2$ Hz, 1H), 7.23 (t, $J = 53.5$ Hz, 1H), 4.33 (dq, $J = 47.7, 9.0$ Hz, 2H), 4.11 - 3.93 (m, 2H), 3.71 (s, 3H), 1.89 (p, $J = 6.4$ Hz, 1H), 1.50 - 1.32 (m, 2H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.93 (d, $J = 6.6$ Hz, 3H); LCMS (ESI) m/e 427.3 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_3$, 427.2]; LC/MS retention time (method B): $t_R = 1.62$ min.

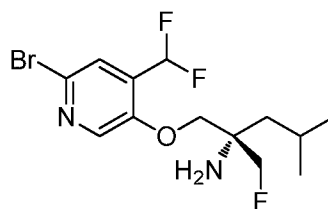
25

Example 181

(*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

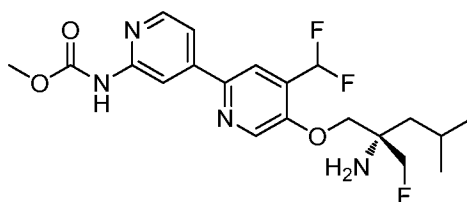


5



Part A: (S)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

Prepared as previously described in Example 19 to afford (*S*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (157 mg, 98%) as a tan oil: ^1H NMR (400 MHz, Methanol- d_4) δ 8.16 (s, 1H), 7.62 (s, 1H), 6.80 (t, J = 54.4 Hz, 1H), 4.35 (ddd, J = 47.4, 36.8, 9.0 Hz, 2H), 4.01 (qd, J = 8.7, 1.7 Hz, 2H), 1.87 (dp, J = 12.9, 6.4 Hz, 1H), 1.48 - 1.43 (m, 2H), 1.03 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H); ^{19}F NMR (376 MHz, Chloroform- d) δ -119.66, -226.04; LCMS (ESI) m/e 355.1 [($\text{M}+\text{H}$) $^+$, calcd $\text{C}_{13}\text{H}_{19}\text{BrF}_3\text{N}_2\text{O}$, 355.1]; LC/MS retention time (method B): t_R = 1.78 min.



Part B: (S)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

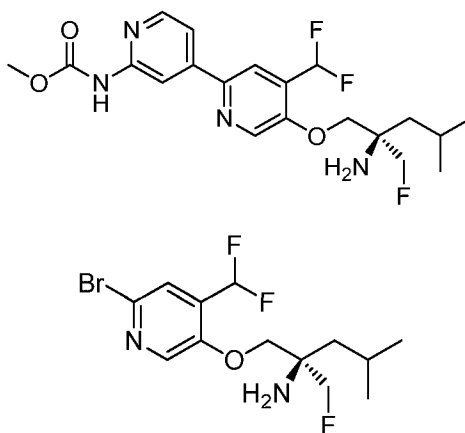
Prepared as previously described for Example 179 to afford the titled product (4.0 mg, 17%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.73 (s, 1H), 8.53 (s, 1H), 8.36 (d, J = 5.2 Hz, 1H), 8.08 (s, 1H), 7.70 (d, J = 5.3 Hz, 1H), 7.35 (t, J = 53.9 Hz, 1H), 4.45 - 4.23 (m, 2H), 4.20 - 4.05 (m, 2H), 3.71 (s, 3H), 1.90 (p, J = 6.5 Hz, 1H), 1.40

(qd, $J = 13.9, 5.7$ Hz, 2H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); LCMS (ESI) m/e 427.3 [(M+H)⁺, calcd C₂₀H₂₆F₃N₄O₃, 427.2]; LC/MS retention time (method B): $t_R = 1.67$ min.

5

Example 182

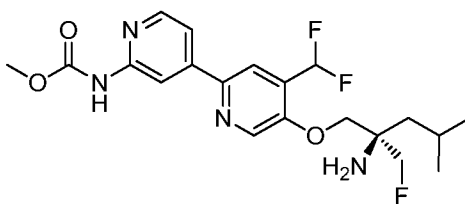
(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



10 *Part A: (R)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine*

Prepared as previously described in Example 19 to afford (*R*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (163 mg, 100%) as a tan oil: ¹H NMR (400 MHz, Methanol-d₄) δ 8.17 (s, 1H), 7.62 (s, 1H), 6.80 (t, $J = 54.4$ Hz, 1H), 4.35 (ddd, $J = 47.5, 36.9, 9.0$ Hz, 2H), 4.01 (qd, $J = 8.7, 1.7$ Hz, 2H), 1.87 (dp, $J = 12.8, 6.4$ Hz, 1H), 1.54 - 1.43 (m, 4H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.00 (d, $J = 6.6$ Hz, 3H); ¹⁹F NMR (376 MHz, Chloroform-d) δ -119.62, -226.06; LCMS (ESI) m/e 355.1 [(M+H)⁺, calcd C₁₃H₁₉BrF₃N₂O, 355.1]; LC/MS retention time (method B): $t_R = 1.79$ min.

20

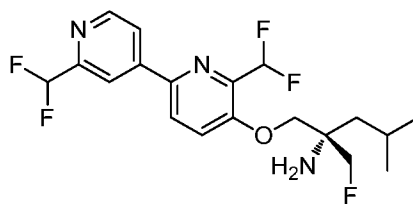


Part B: (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described for Example 179 to afford (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (3.4 mg, 13%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.73 (s, 1H), 8.53 (s, 1H), 8.36 (d, *J* = 5.2 Hz, 1H), 8.08 (s, 1H), 7.70 (d, *J* = 5.3 Hz, 1H), 7.35 (t, *J* = 53.9 Hz, 1H), 4.43 - 4.24 (m, 2H), 4.20 - 4.04 (m, 2H), 3.71 (s, 3H), 1.90 (dt, *J* = 12.6, 6.2 Hz, 1H), 1.40 (qd, *J* = 14.4, 5.7 Hz, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 427.3 [(M+H)⁺, calcd C₂₀H₂₆F₃N₄O₃, 427.2]; LC/MS retention time (method B): *t*_R = 1.65 min.

Example 183

(S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

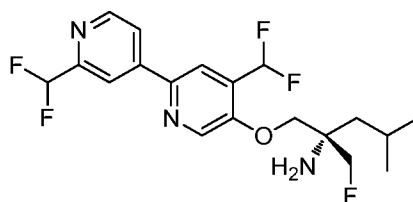


15

Prepared as previously described for Example 179 but for 3 h to afford (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (10 mg, 28%): ¹H NMR (500 MHz, DMSO-d₆) δ 8.80 (d, *J* = 5.1 Hz, 1H), 8.41 (d, *J* = 8.8 Hz, 1H), 8.33 (s, 1H), 8.22 (d, *J* = 5.2 Hz, 1H), 7.88 (d, *J* = 8.9 Hz, 1H), 7.39 - 7.14 (m, 1H), 7.00 (d, *J* = 54.8 Hz, 1H), 4.43 - 4.23 (m, 2H), 4.10 - 3.96 (m, 2H), 1.90 (dt, *J* = 12.8, 6.4 Hz, 1H), 1.49 - 1.32 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H); LCMS (ESI) *m/e* 404.3 [(M+H)⁺, calcd C₁₉H₂₃F₅N₃O, 404.2]; LC/MS retention time (method B): *t*_R = 1.90 min.

Example 184

(S)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

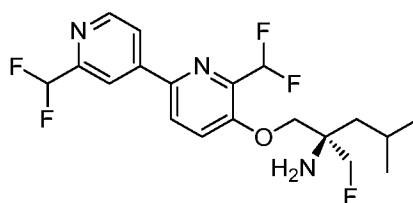


Prepared as previously described for Example 179 but for 3 h to afford (*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (15.1 mg, 45%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.79 (d, J = 5.3 Hz, 1H), 8.76 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.26 (d, J = 5.2 Hz, 1H), 7.35 (t, J = 53.8 Hz, 1H), 7.05 (t, J = 54.9 Hz, 1H), 4.43 - 4.25 (m, 2H), 4.21 - 4.04 (m, 2H), 1.90 (dt, J = 12.8, 6.4 Hz, 1H), 1.48 - 1.33 (m, 2H), 0.96 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H); LCMS (ESI) m/e 404.3 [(M+H) $^+$], calcd $\text{C}_{19}\text{H}_{23}\text{F}_5\text{N}_3\text{O}$, 404.2]; LC/MS retention time (method B): t_R = 1.86 min.

10

Example 185

(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

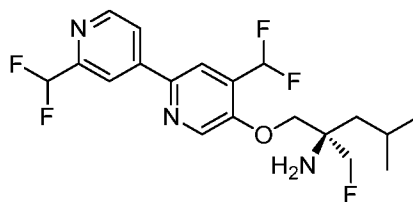


Prepared as previously described for Example 179 but for 3 h to afford (*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (10 mg, 28%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.80 (d, J = 5.1 Hz, 1H), 8.41 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H), 8.22 (d, J = 5.2 Hz, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.40 - 7.15 (m, 1H), 6.99 (d, J = 54.9 Hz, 1H), 4.44 - 4.23 (m, 2H), 4.11 - 3.95 (m, 2H), 1.90 (dt, J = 12.7, 6.3 Hz, 1H), 1.49 - 1.32 (m, 2H), 0.96 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H); LCMS (ESI) m/e 404.3 [(M+H) $^+$], calcd $\text{C}_{19}\text{H}_{23}\text{F}_5\text{N}_3\text{O}$, 404.2]; LC/MS retention time (method B): t_R = 1.87 min.

25

Example 186

(*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

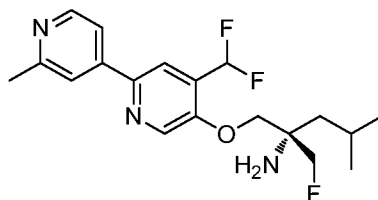


Prepared as previously described for Example 179 to afford (*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (7.7 mg, 16%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.79 (d, *J* = 5.1 Hz, 1H), 8.76 (s, 1H), 8.37 (s, 1H), 8.33 (s, 1H), 8.26 (d, *J* = 5.3 Hz, 1H), 7.35 (t, *J* = 53.8 Hz, 1H), 7.05 (t, *J* = 54.8 Hz, 1H), 4.45 - 4.24 (m, 2H), 4.21 - 4.03 (m, 2H), 1.90 (p, *J* = 6.4 Hz, 1H), 1.50 - 1.33 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 404.3 [(*M*+*H*)⁺, calcd C₁₉H₂₃F₅N₃O, 404.2]; LC/MS retention time (method B): *t*_R = 1.87 min.

10

Example 187

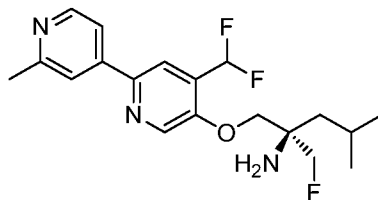
(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



Prepared as previously described for Example 179 to afford (*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (16.8 mg, 50%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.54 (d, *J* = 5.4 Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 5.2 Hz, 1H), 7.34 (t, *J* = 53.9 Hz, 1H), 4.42 - 4.25 (m, 2H), 4.18 - 4.03 (m, 2H), 2.56 (s, 3H), 1.90 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.40 (qd, *J* = 14.3, 5.7 Hz, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); LCMS (ESI) *m/e* 368.3 [(*M*+*H*)⁺, calcd C₁₉H₂₅F₃N₃O, 368.2]; LC/MS retention time (method B): *t*_R = 1.39 min.

Example 188

(*R*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

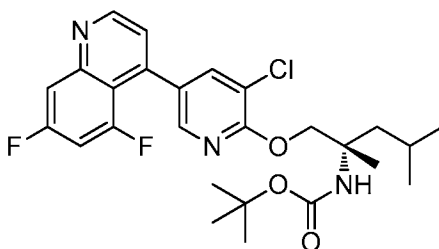
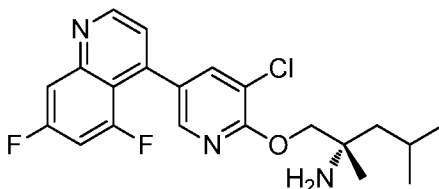


Prepared as previously described for Example 179 to afford (*R*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (20.5 mg, 59%): ^1H NMR (500 MHz, DMSO- d_6) δ 8.71 (s, 1H), 8.54 (d, $J = 5.4$ Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.84 (d, $J = 5.2$ Hz, 1H), 7.34 (t, $J = 53.9$ Hz, 1H), 4.44 - 4.24 (m, 2H), 4.18 - 4.02 (m, 2H), 2.56 (s, 3H), 1.90 (dt, $J = 12.9, 6.3$ Hz, 1H), 1.40 (qd, $J = 14.2, 5.8$ Hz, 2H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H); LCMS (ESI) m/e 368.3 [(M+H) $^+$], calcd C₁₉H₂₅F₃N₃O, 368.2]; LC/MS retention time (method B): $t_R = 1.47$ min.

10

Example 189

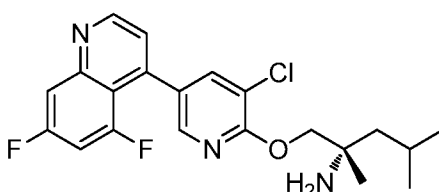
(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide



15 *Part A: (S)-tert-butyl (1-((3-chloro-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Prepared as described in Example 77. Obtained (*S*)-*tert*-butyl (1-((3-chloro-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (33.4 mg, 48%). LCMS (ESI) m/e 506.0 [(M+H) $^+$], calcd C₂₆H₃₁F₂N₃ClO₃, 506.2];

20 LC/MS retention time (method B): $t_R = 2.48$ min.

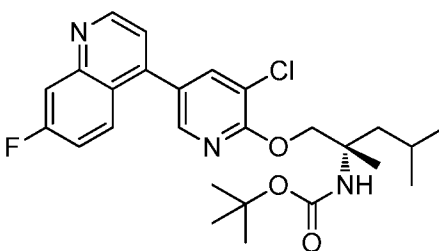
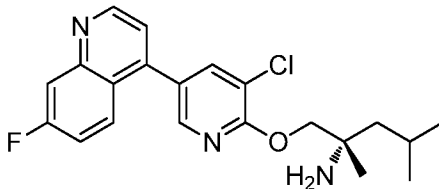


Part B: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

TFA deprotection was carried out as described in Example 32. Obtained (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide (27 mg, 100%) as a colorless solid. ¹H NMR (500 MHz, DMSO-d₆) δ 10.53 (s, 1H), 8.33 (d, *J* = 4.9 Hz, 2H), 7.61 (dd, *J* = 12.5, 2.2 Hz, 1H), 7.52 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.43 - 7.37 (m, 1H), 7.32 (t, *J* = 8.7 Hz, 1H), 3.97 (dd, *J* = 9.5, 4.9 Hz, 1H), 3.90 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.12 (dt, *J* = 11.9, 5.4 Hz, 1H), 2.12 (s, 3H), 1.81 (dq, *J* = 13.0, 6.5 Hz, 1H), 1.33 (ddd, *J* = 13.5, 8.5, 5.0 Hz, 1H), 1.26 (ddd, *J* = 13.5, 8.5, 5.5 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); LCMS (ESI) *m/e* 406.0 [(M+H)⁺, calcd C₂₁H₂₃F₂N₃ClO₁, 406.1]; LC/MS retention time (method B): *t*_R = 2.03 min.

Example 190

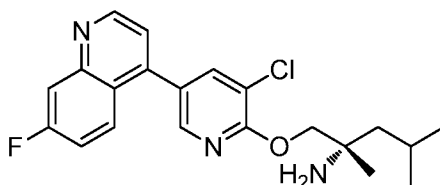
(S)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-tert-butyl (1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Intermediate 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline was prepared as described in Example 77, Part C. Suzuki coupling was performed as described in Example 77, Part D. Obtained (S)-tert-butyl (1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (10.6 mg, 76% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.97 (d, *J*=4.3 Hz, 1H),

8.18 (d, $J=2.0$ Hz, 1H), 7.91 - 7.80 (m, 3H), 7.37 (ddd, $J=9.3, 8.0, 2.5$ Hz, 1H), 7.30 (d, $J=4.0$ Hz, 1H), 4.63 (d, $J=10.5$ Hz, 1H), 4.47 (d, $J=10.5$ Hz, 1H), 1.93 - 1.83 (m, 2H), 1.68 (d, $J=8.8$ Hz, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.02 (m, 6H). ^{19}F NMR (376MHz, CHLOROFORM- d) δ -109.18 (s, 1F). LCMS (ESI) m/e 488.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{26}\text{H}_{32}\text{F}_1\text{N}_3\text{Cl}_1\text{O}_3$, 488.2]; LC/MS retention time (method B): $t_R = 2.39$ min.

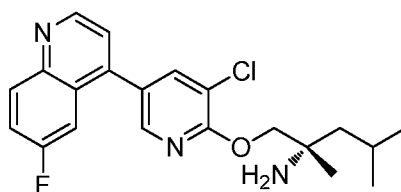


Part B: (S)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection was performed as described in Example 32. Obtained (S)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (4.4 mg, 50% yield). ^1H NMR (600MHz, DMSO- d_6) δ 9.06 - 8.97 (m, 1H), 8.38 - 8.29 (m, 1H), 8.25 - 8.16 (m, 1H), 8.04 - 7.83 (m, 2H), 7.65 - 7.51 (m, 2H), 4.27 - 4.13 (m, 2H), 1.95 - 1.79 (m, 1H), 1.56 - 1.40 (m, 2H), 1.26 - 1.16 (m, 3H), 1.03 - 0.91 (m, 6H). LCMS (ESI) m/e 409.9 $[(\text{M}+\text{Na})^+]$, calcd $\text{C}_{21}\text{H}_{23}\text{F}_1\text{N}_3\text{Cl}_1\text{O}_1\text{Na}_1$, 410.1]; LC/MS retention time (method B): $t_R = 1.85$ min.

Example 191

(S)-1-((3-chloro-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

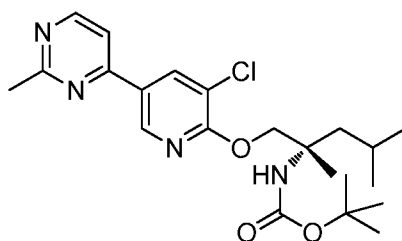
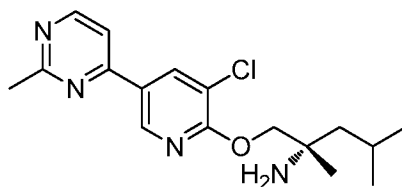


Prepared as described in Example 191 to afford (S)-1-((3-chloro-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (9.4 mg, 0.024 mmol, 50% yield for the final step) as a colorless solid. ^1H NMR (600MHz, DMSO- d_6) δ 9.06 - 8.97 (m, 1H), 8.38 - 8.29 (m, 1H), 8.25 - 8.16 (m, 1H), 8.04 - 7.83 (m, 2H), 7.65 - 7.51 (m, 2H), 4.27 - 4.13 (m, 2H), 1.95 - 1.79 (m, 1H), 1.56 - 1.40 (m, 2H), 1.26 - 1.16 (m, 3H), 1.03 - 0.91 (m, 6H), two exchangeable protons not

observed; LCMS (ESI) m/e 388.1 $[(M+H)^+]$, calcd $C_{21}H_{24}FN_3ClO$, 388.2; LC/MS retention time (method E): t_R = 1.82 min.

Example 192

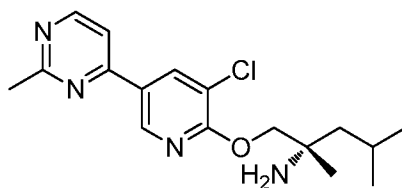
- 5 (S)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



- 10 *Part A: (S)-tert-butyl (1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Intermediate (S)-tert-butyl (1-((3-chloro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate was prepared as described in Example 77, Part C. Suzuki coupling was performed as

- 15 described in Example 77, Part D. (Crude was carried on next step). LCMS (ESI) m/e 457.1 $[(M+Na)^+]$, calcd $C_{23}H_{31}N_4ClO_3Na$, 457.2; LC/MS retention time (method B): t_R = 2.41 min.



- 20 *Part B: (S)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine*

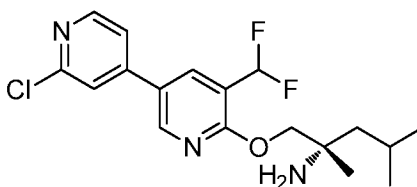
TFA deprotection was performed as described in Example 32 to obtain (S)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine 10.1 mg, 0.030 mmol, 51% yield in two steps). ^1H NMR (500MHz, DMSO- d_6) δ

8.94 (d, $J=2.2$ Hz, 1H), 8.76 (d, $J=5.5$ Hz, 1H), 8.63 (d, $J=1.8$ Hz, 1H), 7.95 (d, $J=5.5$ Hz, 1H), 4.22 - 4.14 (m, 2H), 2.68 (s, 3H), 1.85 - 1.78 (m, 1H), 1.42 (dd, $J=9.0, 5.3$ Hz, 2H), 1.15 (s, 3H), 0.92 (m, 6H); LCMS (ESI) m/e 318.1 [(M-NH₂)⁺, calcd C₁₇H₂₁N₃ClO, 318.1]; LC/MS retention time (method B): t_R = 1.83 min.

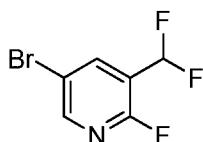
5

Example 193

(*S*)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



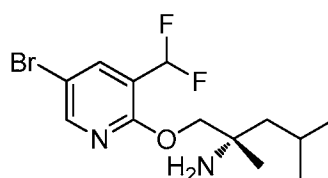
10



Part A: 5-Bromo-3-(difluoromethyl)-2-fluoropyridine

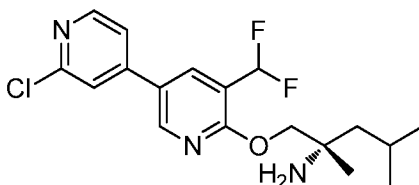
To a solution of 5-bromo-2-fluoronicotinaldehyde (0.8212 g, 4.03 mmol) in CH₂Cl₂ (15 mL) at 0 °C was added DAST (1.064 mL, 8.05 mmol). The reaction was stirred at 0 °C for 1 h then warmed to room temperature. The stirring was continued for 3 h. The reaction was poured into an ice cold 1N NaOH solution. The organic layer was separated and the aqueous layer was extracted DCM (2x). The DCM layers were combined, dried (Na₂SO₄), filtered and concentrated under reduced pressure to give crude 5-bromo-3-(difluoromethyl)-2-fluoropyridine (0.81 g, 3.58 mmol, 89% yield) as a brown solid. ¹H NMR (400MHz, CHLOROFORM-d) δ 8.43 - 8.38 (m, 1H), 8.18 - 8.13 (m, 1H), 6.82 (t, $J=52.0$ Hz, 1H); ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -74.33 (br. s., 1F), -115.87 (s, 2F); LCMS (ESI) m/e 205.9 [(M-F)⁺, calcd C₆H₃BrNF₂, 205.9]; LC/MS retention time (method B): t_R = 1.88 min.

25



Part B: (S)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

To (S)-2-amino-2,4-dimethylpentan-1-ol (0.3359 g, 2.56 mmol) and 5-bromo-3-(difluoromethyl)-2-fluoropyridine (0.579 g, 2.56 mmol) in THF (5 mL) at room temperature was added potassium *tert*-butoxide (3.07 mL, 3.07 mmol). The reaction was stirred at room temperature overnight. The reaction was quenched by addition of water and the crude solution was diluted with ethyl acetate. The ethyl acetate layer was separated and washed with water (3x), dried (Na₂SO₄), filtered and concentrated under reduced pressure. The product was purified by silica gel chromatography (eluted with 0- 10% methanol in CH₂Cl₂) to obtain (S)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.63 g, 0.923 mmol, 73% yield) as a yellow liquid. ¹H NMR (400MHz, CHLOROFORM-d) δ 8.31 - 8.27 (m, 1H), 7.96 - 7.93 (m, 1H), 6.97 - 6.64 (m, 1H), 4.15 (s, 2H), 1.85 - 1.74 (m, 1H), 1.45 (t, *J*=5.8 Hz, 2H), 1.20 (s, 3H), 0.98 (m, 6H). ¹⁹F NMR (376MHz, CHLOROFORM-d) δ -117.61 (s, 2F); LCMS (ESI) *m/e* 320.1 [(M-NH₂)⁺, calcd C₁₃H₁₇BrNF₂O, 320.1]; LC/MS retention time (method B): *t*_R = 1.99 min.



Part C: (S)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine

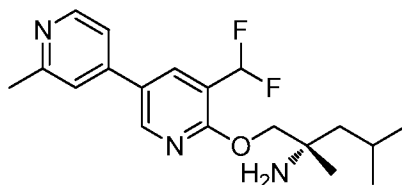
A mixture of 2N sodium carbonate solution (0.050 mL, 0.099 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (2.022 mg, 2.476 μmol), 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.018 g, 0.074 mmol) and (S)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0167 g, 0.050 mmol) in dioxane (0.8 mL) (degassed) was heated at 80 °C for 2 h. The reaction was filtered through celite and purified by reverse phase Prep HPLC. Obtained (S)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (13.1 mg, 0.035 mmol, 72% yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 8.83 (s, 1H), 8.48 (d, *J*=5.1 Hz, 1H), 8.43 (s, 1H), 7.98 (s, 1H), 7.84 (d, *J*=4.8 Hz, 1H), 7.27 (t, *J*=55.0 Hz,

1H), 4.22 - 4.14 (m, 2H), 1.83 - 1.73 (m, 1H), 1.48 - 1.37 (m, 2H), 1.15 (s, 3H), 0.91 (m, 6H). LCMS (ESI) m/e 353.1 [(M-NH₂)⁺, calcd C₁₈H₂₀N₂ClF₂O, 353.1]; LC/MS retention time (method B): t_R = 1.96 min.

5

Example 194

(*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine

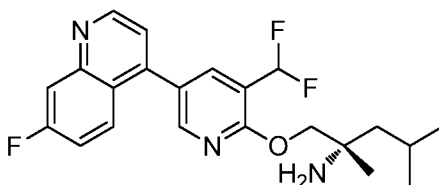


Prepared as described in Example 193 to afford (*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (9.2 mg, 0.026 mmol, 45% yield for the final step) as a colorless solid. ¹H NMR (500MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.50 (d, J =5.2 Hz, 1H), 8.33 (s, 1H), 7.66 (s, 1H), 7.57 (d, J =4.9 Hz, 1H), 7.45 - 7.11 (m, 1H), 4.24 - 4.11 (m, 2H), 2.53 (s, 3H), 1.82 - 1.72 (m, 1H), 1.44 (qd, J =13.9, 5.5 Hz, 2H), 1.16 (s, 3H), 0.92 (d, J =6.7 Hz, 3H), 0.89 (d, J =6.4 Hz, 3H) two exchangeable protons not observed; LCMS (ESI) m/e 350.0 [(M+H)⁺, calcd C₁₉H₂₆F₂N₃O, 350.2]; LC/MS retention time (method E): t_R = 2.62 min.

20

Example 195

(*S*)-1-((3-(difluoromethyl)-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-1-((3-(difluoromethyl)-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

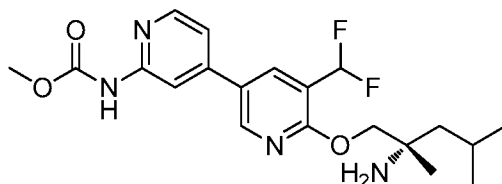
25

Intermediate 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline was prepared as described in Example 77, Part C. Final product was prepared as described in Example 193 to obtain (*S*)-1-((3-(difluoromethyl)-5-(7-

fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (13.9 mg, 0.034 mmol, 34% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.00 (d, *J*=4.4 Hz, 1H), 8.51 (s, 1H), 8.15 (s, 1H), 7.97 - 7.85 (m, 2H), 7.59 (td, *J*=8.8, 2.6 Hz, 1H), 7.56 (d, *J*=4.4 Hz, 1H), 7.28 (t, *J*=55.0 Hz, 1H), 4.18 (s, 2H), 1.86 - 1.76 (m, 1H), 1.48 - 1.36 (m, 2H), 1.15 (s, 3H), 0.94 (m, 6H); LCMS (ESI) *m/e* 387.1 [(M-NH₂)⁺, calcd C₂₂H₂₂N₂F₃O, 387.2]; LC/MS retention time (method B): *t*_R = 1.86 min.

Example 196

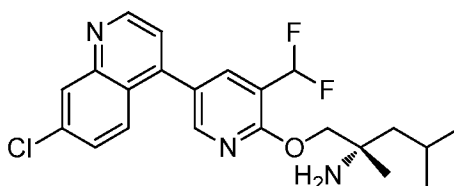
(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate



Prepared as described in Example 193. Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate (8.0mg, 0.018 mmol, 40% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.56 (br. s., 1H), 8.34 (d, *J*=4.8 Hz, 1H), 8.24 (br. s., 1H), 8.13 (br. s., 2H), 7.19 (d, *J*=3.8 Hz, 1H), 7.11 - 6.73 (m, 1H), 4.26 (br. s., 2H), 3.85 (s, 3H), 1.77 (m 1H), 1.50 (br. s., 2H), 1.25 (br. s., 3H), 1.00 (t, *J*=7.4 Hz, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 431.1 [(M+Na)⁺, calcd C₂₀H₂₆N₄F₂O₃Na, 431.2]; LC/MS retention time (method B): *t*_R = 1.78 min.

Example 197

(*S*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

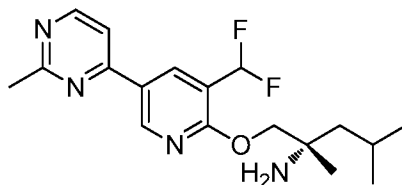


Intermediate (*S*)-1-((3-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine was prepared as described in Example 77, Part C. Intermediate 4-bromo-7-chloroquinoline was

prepared as described in Example 77, Part B. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (7.8 mg, 0.019 mmol, 34% yield). ¹H NMR (500MHz, DMSO-*d*₆) δ 9.02 (d, *J*=4.6 Hz, 1H), 8.53 (s, 1H), 8.20 (d, *J*=1.8 Hz, 1H), 8.16 (s, 1H), 7.88 (d, *J*=9.2 Hz, 1H), 7.69 (dd, *J*=9.0, 2.0 Hz, 1H), 7.61 (d, *J*=4.3 Hz, 1H), 7.29 (t, *J*=55.0 Hz, 1H), 4.22 - 4.16 (m, 2H), 1.83 (dt, *J*=12.5, 6.3 Hz, 1H), 1.49 - 1.38 (m, 2H), 1.17 (s, 3H), 0.97 - 0.92 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 442.0 [(*M*+Na)⁺, calcd C₂₂H₂₄ClN₃F₂ONa, 442.2]; LC/MS retention time (method B): *t*_R = 2.09 min.

Example 198

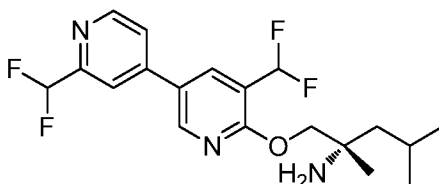
(*S*)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Intermediate (*S*)-1-((3-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (7.7 mg, 0.036 mmol, 37% yield). ¹H NMR (500MHz, DMSO-*d*₆) δ 9.13 (s, 1H), 8.78 (d, *J*=5.2 Hz, 1H), 8.69 (s, 1H), 7.99 (d, *J*=5.2 Hz, 1H), 7.29 (t, *J*=55.0 Hz, 1H), 4.19 (d, *J*=1.8 Hz, 2H), 2.70 (s, 3H), 1.85 - 1.76 (m, 1H), 1.46 - 1.36 (m, 2H), 1.14 (s, 3H), 0.92 (m, 6H); LCMS (ESI) *m/e* 334.1 [(*M*-NH₂)⁺, calcd C₁₈H₂₂N₃F₂O, 334.2]; LC/MS retention time (method B): *t*_R = 1.91 min.

Example 199

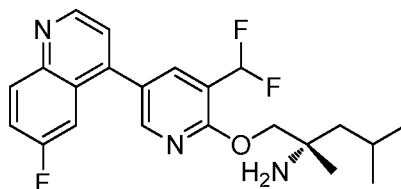
(*S*)-1-((2',5-bis(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



5 Intermediate (*S*)-1-((3-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((2',5-bis(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (9.2 mg, 0.023 mmol, 39% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.86 (s, 1H), 8.77 (d, *J*=5.2 Hz, 1H), 8.45 (s, 1H), 8.10 (s, 1H), 8.00 (d, *J*=4.6 Hz, 1H), 7.26 (t, *J*=55.0 Hz, 1H), 7.02 (t, *J*=55.0 Hz, 1H), 4.18 (d, *J*=1.8 Hz, 2H), 1.85 - 1.75 (m, 1H), 1.48 - 1.36 (m, 2H), 1.15 (s, 3H), 0.94 (d, *J*=6.7 Hz, 3H), 0.92 (d, *J*=6.7 Hz, 3H), two exchangeable protons not observed; LCMS (ESI) *m/e* 369.1 [(M-NH₂)⁺, calcd C₁₉H₂₁N₂F₄O, 369.2]; LC/MS retention time (method B): *t*_R = 1.91 min.

Example 200

(*S*)-1-((3-(difluoromethyl)-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



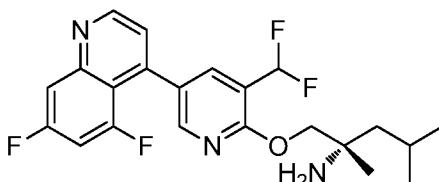
20 Intermediate 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline was prepared as described in Example 77, Part B and C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((3-(difluoromethyl)-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (27.2 mg, 0.067 mmol, 39% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.97 (d, *J*=4.4 Hz, 1H), 8.52 (s, 1H), 8.22 (dd, *J*=9.2, 5.9 Hz, 1H), 8.16 (s, 1H), 7.81 - 7.72 (m, 1H), 7.61 (d, *J*=4.4 Hz, 1H), 7.51 (dd, *J*=10.1, 2.8 Hz, 1H), 7.28 (t, *J*=55.0 Hz, 1H), 4.19 (s, 2H),

1.86 - 1.77 (m, 1H), 1.49 - 1.37 (m, 2H), 1.16 (s, 3H), 0.94 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 426.2 $[(M+Na)^+]$, calcd $C_{22}H_{24}N_3F_3ONa$, 426.2]; LC/MS retention time (method B): t_R = 1.93 min.

5

Example 201

(*S*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

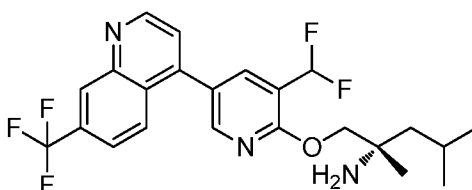


Intermediate (*S*)-*tert*-butyl 1-((3-chloro-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate was prepared in Example 189. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (13.0 mg, 0.031 mmol, 37% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.02 (d, J =4.4 Hz, 1H), 8.43 (s, 1H), 8.10 (br. s., 1H), 7.80 (d, J =8.4 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.51 (d, J =4.4 Hz, 1H), 7.25 (t, J =55.0 Hz, 1H), 4.16 (s, 2H), 1.81 (dt, J =12.5, 6.2 Hz, 1H), 1.41 (t, J =6.4 Hz, 2H), 1.14 (s, 3H), 0.93 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 405.7 $[(M-NH_2)^+]$, calcd $C_{22}H_{21}N_2F_4O$, 405.2]; LC/MS retention time (method B): t_R = 2.02 min.

15

Example 202

(*S*)-1-((3-(difluoromethyl)-5-(7-(trifluoromethyl)quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



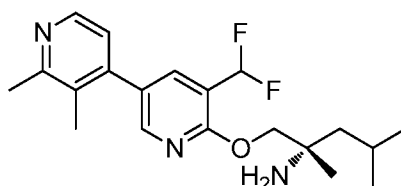
Intermediate 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-(trifluoromethyl)quinoline was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((3-(difluoromethyl)-5-(7-(trifluoromethyl)quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (25.3 mg, 0.055 mmol, 37% yield). ^1H NMR (500MHz,

25

DMSO- d_6) δ 9.14 (d, $J=4.4$ Hz, 1H), 8.56 (s, 1H), 8.48 (s, 1H), 8.20 (s, 1H), 8.08 (d, $J=8.8$ Hz, 1H), 7.92 (d, $J=8.8$ Hz, 1H), 7.75 (d, $J=4.4$ Hz, 1H), 7.29 (t, $J=55.0$ Hz, 1H), 4.20 (s, 2H), 1.87 - 1.79 (m, 1H), 1.49 - 1.38 (m, 2H), 1.16 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 437.1 [(M-NH $_2$) $^+$, calcd C $_{23}$ H $_{22}$ N $_2$ F $_5$ O, 437.2]; LC/MS retention time (method B): t_R = 2.13 min.

Example 203

(*S*)-1-((5-(difluoromethyl)-2',3'-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



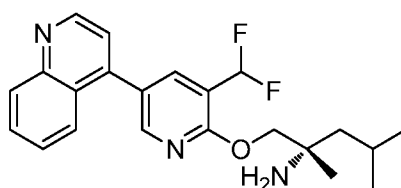
10

Intermediate 2,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((5-(difluoromethyl)-2',3'-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (20.4 mg, 0.056 mmol, 26% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.32 (d, $J=4.0$ Hz, 2H), 7.95 (s, 1H), 7.38 - 7.11 (m, 2H), 4.15 (s, 2H), 2.52 (br. s., 3H), 2.17 (s, 3H), 1.84 - 1.75 (m, 1H), 1.42 (dd, $J=10.5, 5.3$ Hz, 2H), 1.15 (s, 3H), 0.93 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 347.1 [(M-NH $_2$) $^+$, calcd C $_{20}$ H $_{25}$ N $_2$ F $_2$ O, 347.2]; LC/MS retention time (method B): t_R = 1.48 min.

20

Example 204

(*S*)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



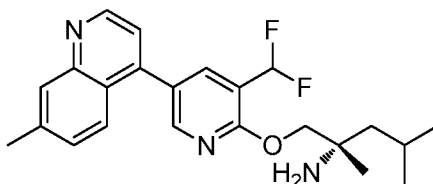
25

Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (17.4 mg, 0.045 mmol 66% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.05 (d, $J=4.0$

Hz, 1H), 8.57 (br. s., 1H), 8.34 (br. s., 2H), 8.21 (br. s., 1H), 8.18 (d, $J=8.5$ Hz, 1H), 7.89 (t, $J=7.5$ Hz, 1H), 7.85 (d, $J=8.5$ Hz, 1H), 7.70 (t, $J=7.5$ Hz, 1H), 7.65 (d, $J=4.3$ Hz, 1H), 7.63 - 7.40 (m, 1H), 4.64-4.39 (m, 2H), 1.89 - 1.73 (m, 2H), 1.65 (dd, $J=13.7, 4.6$ Hz, 1H), 1.42 (s, 3H), 0.97 (d, $J=6.4$ Hz, 3H), 0.93 (d, $J=6.1$ Hz, 3H);
 5 LCMS (ESI) m/e 386.1 $[(M+H)^+]$, calcd $C_{22}H_{26}N_3F_2O$, 386.2]; LC/MS retention time (method B): $t_R = 1.68$ min.

Example 205

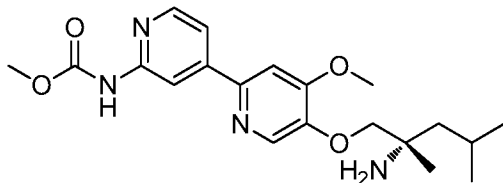
(*S*)-1-((3-(difluoromethyl)-5-(7-methylquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
 10 dimethylpentan-2-amine



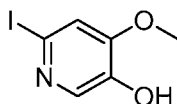
A mixture of 2N sodium carbonate solution (0.146 mL, 0.291 mmol), (*S*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0611 g, 0.146 mmol) (Example 197), 2,4,6-trimethyl-1,3,5,2,4,6-
 15 trioxatriborinane (0.018 g, 0.146 mmol) and 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (5.94 mg, 7.28 μ mol) in dioxane (1 mL) (degassed) was heated at 110 °C for 3 h. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The product was
 20 purified by reverse phase Prep HPLC to afford (*S*)-1-((3-(difluoromethyl)-5-(7-methylquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (1.1 mg, 2.5 mol, 2% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.93 (d, $J=4.4$ Hz, 1H), 8.51 (s, 1H), 8.13 (s, 1H), 7.93 (s, 1H), 7.73 (d, $J=8.8$ Hz, 1H), 7.53 - 7.47 (m, 2H), 7.32 (t, $J=55.0$ Hz, 1H), 2.56 (s, 3H), 1.87 - 1.79 (m, 1H), 1.54 - 1.41 (m, 2H), 1.20 (s, 3H),
 25 0.95 (m, 6H). (NMR water suppression also suppressed OCH_2 ether signal); LCMS (ESI) m/e 400.2 $[(M+H)^+]$, calcd $C_{23}H_{28}N_3F_2O$, 400.2]; LC/MS retention time (method B): $t_R = 1.72$ min.

Example 206

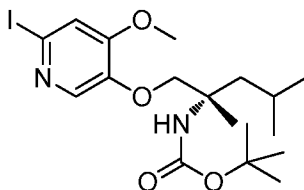
(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate



5

*Part A: 6-Iodo-4-methoxypyridin-3-ol*

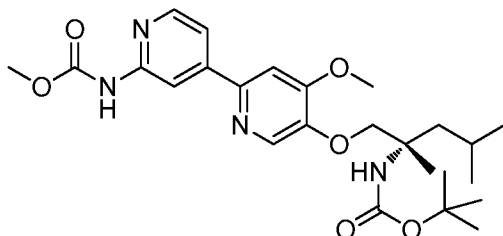
n- BuLi (0.319 mL, 0.797 mmol) was added to the THF (4 mL) solution of
 10 2,6-diiodo-4-methoxypyridin-3-yl diethylcarbamate (0.316 g, 0.664 mmol) (Ref:
J.Org. Chem. **2002**, 67, 3272-3276) at -78 °C. After stirring at -78 °C for 20 min, the
 reaction was quenched by addition of NH₄Cl (sat.). The reaction was warmed to
 room temperature and stirred for another 30 min. The volatiles were removed under
 reduced pressure and the crude material was partitioned between ethyl acetate and
 15 water. The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and
 concentrated under reduced pressure. The residue was purified via silica gel
 chromatography (eluted with 0-25% ethyl acetate in hexanes) to give 6-iodo-4-
 methoxypyridin-3-ol (0.033 g, 0.131 mmol, 20% yield). ¹H NMR (400MHz,
 CHLOROFORM-d) δ 7.95 (s, 1H), 7.14 (s, 1H), 3.92 (s, 3H), one exchangeable
 20 proton was not observed; LCMS (ESI) *m/e* 251.9 [(M+H)⁺, calcd C₆H₇INO₂, 252.0];
 LC/MS retention time (method B): *t*_R = 0.85 min.



25

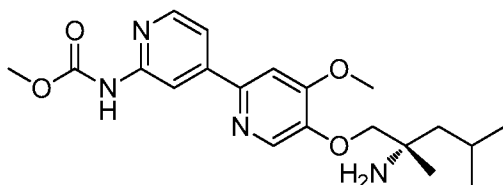
Part B: (S)-tert-butyl (1-((6-iodo-4-methoxypyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Preparation was described as Example 53, Part A. The crude material was carried on without further purification. LCMS (ESI) m/e 465.0 $[(M+H)^+]$, calcd $C_{18}H_{30}IN_2O_4$, 465.1]; LC/MS retention time (method B): t_R = 2.24 min.



Part C: Boc protected (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate

Suzuki reaction was performed as described in Example 193. Obtained Boc protected (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate (2.3 mg, 4.71 μ mol, 22% yield for two steps). LCMS (ESI) m/e 489.3 $[(M+H)^+]$, calcd $C_{25}H_{37}N_4O_6$, 489.2]; LC/MS retention time (method B): t_R = 2.14 min.

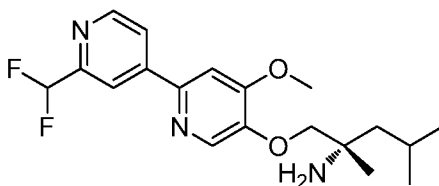


Part D: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate

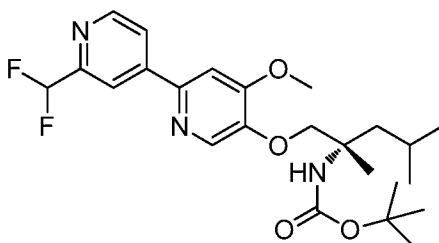
TFA deprotection was performed as described in Example 32. Obtained (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate (1.2 mg, 3.09 μ mol, 66% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.51 (s, 1H), 8.34 (d, J =5.1 Hz, 1H), 8.31 (s, 1H), 7.69 (d, J =5.1 Hz, 1H), 7.59 (s, 1H), 3.99 (s, 3H), 3.83 (s, 2H), 3.70 (s, 3H), 3.41 (br. s., 2H), 1.85 - 1.75 (m, 1H), 1.39 (dd, J =9.0, 5.7 Hz, 2H), 1.12 (s, 3H), 0.93 (m, 6H), one exchangeable proton not observed. LCMS (ESI) m/e 389.3 $[(M+H)^+]$, calcd $C_{20}H_{29}N_4O_4$, 389.2]; LC/MS retention time (method B): t_R = 1.56 min.

Example 207

(*S*)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

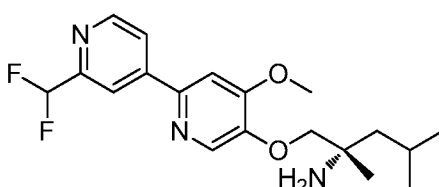


5



Part A: (S)-tert-butyl (1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki reaction was performed as described in Example 193 to afford (*S*)-
 10 *tert*-butyl (1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (12.9 mg, 0.028 mmol, 13% yield). LCMS (ESI) *m/e* 466.2 [(M+H)⁺, calcd C₂₄H₃₄F₂N₃O₄, 466.2]; LC/MS retention time (method B): *t*_R = 2.65 min.



15

Part B: (S)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

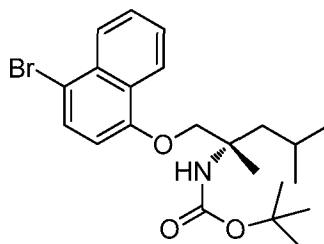
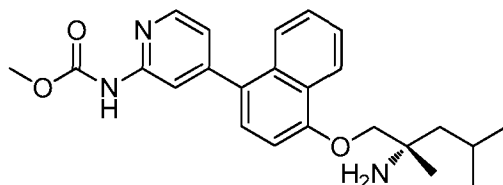
TFA deprotection was performed as described in Example 32. Obtained (*S*)-1-
 20 ((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (5.0 mg, 0.014 mmol, 53% yield). ¹H NMR (500MHz, DMSO-*d*₆) δ 8.78 (d, *J*=4.8 Hz, 1H), 8.38 (s, 2H), 8.26 (d, *J*=4.8 Hz, 1H), 7.84 (s, 1H), 7.03 (t, *J*=1.0 Hz, 1H), 4.03 (s, 3H), 3.96 (s, 2H), 1.85 - 1.75 (m, 1H), 1.56 - 1.42 (m, 2H), 1.21 (s, 3H),

0.94 (m, 6H), two exchangeable protons not observed. LCMS (ESI) m/e 366.2 $[(M+H)^+]$, calcd $C_{19}H_{26}F_2N_3O_2$, 366.2]; LC/MS retention time (method B): t_R = 1.70 min.

5

Example 208

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

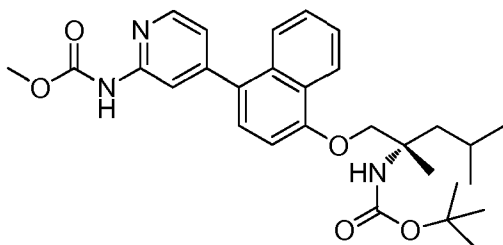


10

Part A: (S)-tert-butyl (1-((4-bromonaphthalen-1-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

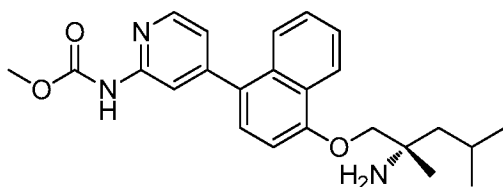
Prepared as described in Example 53, Part A. Obtained (*S*)-tert-butyl (1-((4-bromonaphthalen-1-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (37 mg, 0.085 mmol, 19% yield). ^1H NMR (400MHz, CHLOROFORM- d) δ 8.29 (dd, J =7.8, 0.8 Hz, 1H), 8.18 (d, J =8.0 Hz, 1H), 7.67 - 7.35 (m, 3H), 6.73 (d, J =8.3 Hz, 1H), 4.28 (d, J =9.0 Hz, 1H), 4.13 (d, J =9.0 Hz, 1H), 1.86 (d, J =6.5 Hz, 2H), 1.69 (dd, J =13.9, 5.1 Hz, 1H), 1.51 (s, 3H), 1.42 - 1.38 (m, 9H), 1.01 (m, 6H); LCMS (ESI) m/e 458.1, 460.1 Br pattern $[(M+Na)^+]$, calcd $C_{22}H_{30}BrNNaO_3$, 458.1]; LC/MS retention time (method B): t_R = 2.60 min.

20



Part B: Boc protected (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

Prepared as described in Example 77, Part D. Obtained Boc protected (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate (12.0 mg, 0.024 mmol, 69% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.37 (d, $J=5.8$ Hz, 2H), 8.16 (s, 1H), 7.94 - 7.90 (m, 1H), 7.58 - 7.49 (m, 2H), 7.38 (d, $J=8.0$ Hz, 1H), 7.15 (dd, $J=5.1, 1.4$ Hz, 1H), 6.91 (d, $J=8.0$ Hz, 1H), 4.33 (d, $J=9.0$ Hz, 1H), 4.22 - 4.17 (m, 1H), 3.82 (s, 3H), 1.94 - 1.83 (m, 1H), 1.73 (br. s., 2H), 1.42 (s, 9H), 1.52 (s, 3H), 1.03 (m, 6H), two exchangeable protons not observed. LCMS (ESI) m/e 508.2 [(M+H)⁺, calcd C₂₉H₃₈N₃O₅, 508.3]; LC/MS retention time (method B): t_R = 2.30 min.

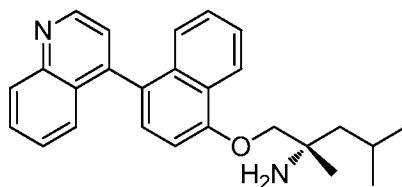


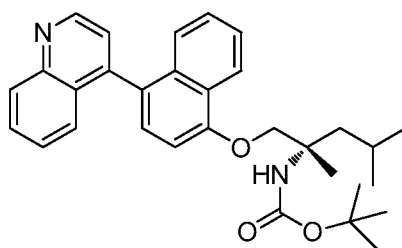
Part C: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

TFA deprotection was performed as described in Example 32. Obtained (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate (9.2 mg, 0.022 mmol, 95% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.40 (d, $J=7.7$ Hz, 1H), 8.37 (d, $J=4.8$ Hz, 1H), 7.95 (s, 1H), 7.85 (d, $J=8.4$ Hz, 1H), 7.59 (t, $J=8.4$ Hz, 2H), 7.42 (d, $J=7.7$ Hz, 1H), 7.16 (d, $J=5.1$ Hz, 1H), 7.06 (d, $J=8.1$ Hz, 1H), 3.94 (s, 2H), 3.67 (s, 3H), 1.86 (d, $J=6.6$ Hz, 1H), 1.54 (dd, $J=9.7, 5.7$ Hz, 2H), 1.25 (s, 3H), 0.94 (m, 6H), three exchangeable protons not observed. LCMS (ESI) m/e 408.2 [(M+H)⁺, calcd C₂₄H₃₀N₃O₃, 408.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 209

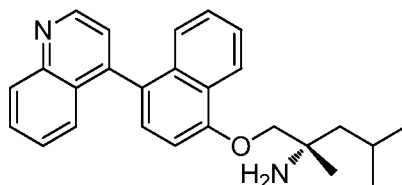
(S)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine





Part A: (S)-tert-butyl (2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-yl)carbamate

5 Prepared as described in Example 77, Part D. Obtained (S)-tert-butyl (2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-yl)carbamate (8.0 mg, 0.014 mmol, 40% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 9.03 (d, *J*=4.3 Hz, 1H), 8.41 (d, *J*=8.5 Hz, 1H), 8.23 (d, *J*=8.5 Hz, 1H), 7.73 (ddd, *J*=8.4, 6.9, 1.5 Hz, 1H), 7.56 - 7.48 (m, 2H), 7.43 (d, *J*=4.3 Hz, 1H), 7.41 - 7.33 (m, 4H), 6.99 (d, *J*=7.8 Hz, 1H), 4.39 (dd, *J*=8.4, 4.6 Hz, 1H), 4.25 (d, *J*=6.5 Hz, 1H), 1.97 - 1.88 (m, 1H), 1.81 - 1.72 (m, 2H), 1.57 (s, 3H), 1.43 (s, 9H), 1.08 - 1.03 (m, 6H), one
10 exchangeable proton not observed; LCMS (ESI) *m/e* 485.2 [(M+H)⁺, calcd C₃₁H₃₇N₂O₃, 485.3]; LC/MS retention time (method B): *t_R* = 2.26 min.



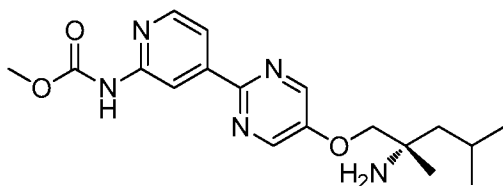
15

Part B: (S)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine

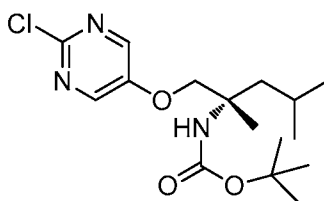
TFA deprotection was performed as described in Example 32. Obtained (S)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine (6.3 mg, 0.016 mmol, 98% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.03 (d, *J*=4.4 Hz, 1H), 8.44 (d, *J*=6.2 Hz, 1H), 8.15 (d, *J*=8.4 Hz, 1H), 7.78 (t, *J*=7.5 Hz, 1H), 7.58 (t, *J*=7.5 Hz, 1H), 7.52 (d, *J*=4.0 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.43 - 7.39 (m, 1H), 7.35 (d, *J*=8.4 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J*=7.7 Hz, 1H), 4.00 (s, 2H), 1.90 - 1.85 (m, 1H), 1.65 - 1.50 (m, 2H), 1.29 (s, 3H), 1.01 - 0.94 (m, 6H), two
20 exchangeable protons not observed; LCMS (ESI) *m/e* 385.2 [(M+H)⁺, calcd C₂₆H₂₉N₂O, 385.2]; LC/MS retention time (method B): *t_R* = 1.70 min.

Example 210

(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate



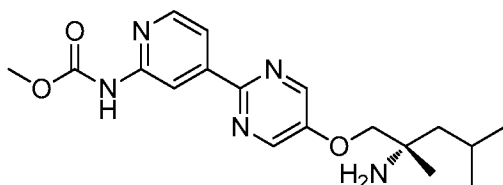
5



Part A: (S)-tert-butyl (1-((2-chloropyrimidin-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 53, Part A. Obtained (*S*)-tert-butyl (1-((2-chloropyrimidin-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (25.0 mg, 0.073 mmol, 49% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.32 (s, 2H), 4.50 (s, 1H), 4.30 (d, *J*=8.5 Hz, 1H), 4.06 (d, *J*=8.8 Hz, 1H), 1.93 - 1.74 (m, 2H), 1.44 (dd, *J*=13.9, 4.9 Hz, 1H), 1.39 (s, 9H), 1.36 (s, 3H), 0.99 (dd, *J*=6.5, 4.5 Hz, 6H).

15



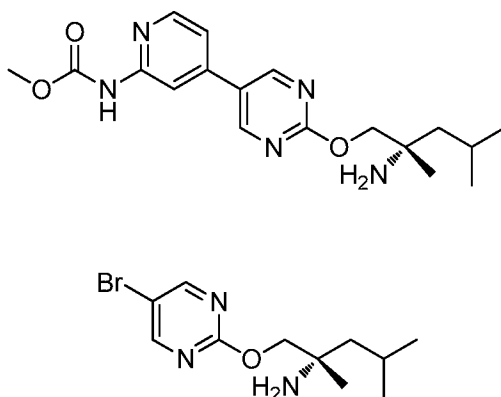
Part B: (S)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate

A mixture of 2N sodium carbonate solution (0.073 mL, 0.145 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (2.97 mg, 3.64 μmol), (*S*)-tert-butyl (1-((2-chloropyrimidin-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate and (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.025 g, 0.128 mmol) in dioxane (1 mL) (degassed) was heated at 120 °C for 4 h. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated

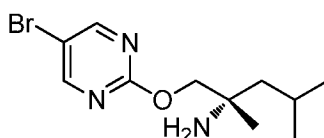
under reduced pressure. The crude material was diluted with DCM (3 mL) and TFA (2 mL, 26.0 mmol) was added at room temperature. The mixture was stirred for 0.5 h at room temperature. The solvent was removed under reduced pressure and the crude was purified by reverse phase Prep HPLC. Obtained (*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate (1.9 mg, 5.07 mol, 7% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.73 (s, 2H), 8.39 (d, *J*=5.5 Hz, 1H), 7.86 (d, *J*=5.1 Hz, 1H), 3.96 (s, 2H), 3.71 (s, 3H), 1.86 - 1.78 (m, 1H), 1.46 - 1.36 (m, 2H), 1.15 (s, 3H), 0.94 (m, 6H), three exchangeable protons not observed. LCMS (ESI) *m/e* 360.1 [(M+H)⁺, calcd C₁₈H₂₆N₅O₃, 360.4]; LC/MS retention time (method B): *t*_R = 1.55 min.

Example 211

(*S*)-methyl (4-(2-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-5-yl)pyridin-2-yl)carbamate



15

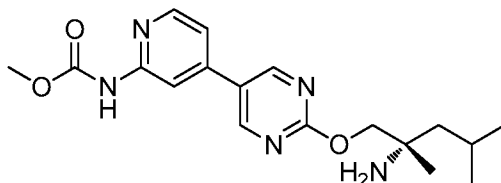


Part A: (*S*)-1-((5-bromopyrimidin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Potassium *tert*-butoxide (0.242 mL, 0.242 mmol) was added to a solution of (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.0265 g, 0.202 mmol) in THF (0.8 mL) at room temperature. After 5 min, 5-bromo-2-chloropyrimidine (0.047 g, 0.242 mmol) was added to the reaction mixture. The reaction was stirred at room temperature overnight. The reaction was quenched by adding water. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and water. The ethyl acetate layer was separated and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layers were combined, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified via silica gel chromatography (eluted with methanol in DCM from 0 to 10%). Obtained (*S*)-1-((5-

25

bromopyrimidin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.014 g, 0.050 mmol, 25% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.53 (s, 2H), 4.11 (d, *J*=2.8 Hz, 2H), 1.87 - 1.75 (m, 1H), 1.66 - 1.56 (m, 2H), 1.48 (dd, *J*=5.6, 3.9 Hz, 2H), 1.22 (s, 3H), 0.98 (m, 6H). LCMS (ESI) *m/e* 310.1 [(M+Na)⁺, calcd C₁₁H₁₈BrN₃ONa, 310.1]; LC/MS retention time (method B): *t*_R = 1.67 min.



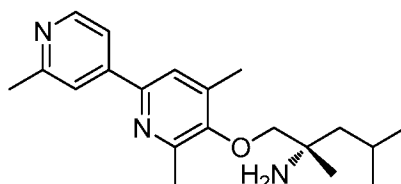
Part B: (S)-methyl (4-(2-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-5-yl)pyridin-2-yl)carbamate

Suzuki reaction was performed as described in Example 193. Obtained (S)-methyl (4-(2-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-5-yl)pyridin-2-yl)carbamate (8.4 mg, 0.023 mmol, 47% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.60 (s, 2H), 8.49 (s, 1H), 8.31 (dd, *J*=5.3, 0.5 Hz, 1H), 8.18 (s, 1H), 7.11 (dd, *J*=5.4, 1.6 Hz, 1H), 3.85 (s, 3H), 3.84 - 3.69 (m, 2H), 2.00 - 1.92 (m, 1H), 1.91 - 1.78 (m, 1H), 1.56 (dd, *J*=14.3, 5.0 Hz, 1H), 1.36 (s, 3H), 1.02 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.5 Hz, 3H), two exchangeable protons not observed; LCMS (ESI) *m/e* 359.9 [(M+H)⁺, calcd C₁₈H₂₆N₅O₃, 360.2]; LC/MS retention time (method B): *t*_R = 1.76 min.

20

Example 212

(S)-2,4-dimethyl-1-((2',4,6-trimethyl-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine



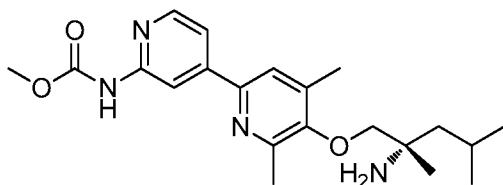
Suzuki reaction was performed as described in Example 193. Obtained (S)-2,4-dimethyl-1-((2',4,6-trimethyl-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine (10.3 mg, 0.031 mmol, 57% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.57 (d, *J*=5.3 Hz, 1H), 7.75 (s, 1H), 7.62 (dd, *J*=5.1, 1.4 Hz, 1H), 7.46 (s, 1H), 3.66 - 3.55 (m, 2H), 2.64 (s, 3H), 2.60 (s, 3H), 2.39 (s, 3H), 2.08 (br. S, 2H); 1.88 (tt, *J*=12.7, 6.4 Hz, 1H),

1.54 (d, $J=5.8$ Hz, 2H), 1.34 (s, 3H), 1.04 (d, $J=6.5$ Hz, 3H), 1.02 (d, $J=6.8$ Hz, 3H); LCMS (ESI) m/e 328.1 $[(M+H)^+]$, calcd $C_{20}H_{30}N_3O$, 328.2]; LC/MS retention time (method B): $t_R = 1.44$ min.

5

Example 213

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4,6-dimethyl-[2,4'-bipyridin]-2'-yl)carbamate

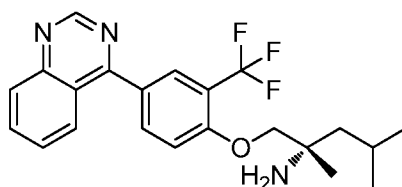


Suzuki reaction was performed as described in Example 193. Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4,6-dimethyl-[2,4'-bipyridin]-2'-yl)carbamate (8.0 mg, 0.021 mmol, 38% yield). ^1H NMR (400MHz, CHLOROFORM- d) δ 8.52 (br. s, 2H), 8.33 - 8.17 (m, 1H), 7.68 (dd, $J=5.3$, 1.5 Hz, 1H), 7.53 (s, 1H), 3.85 (s, 3H), 3.65 - 3.52 (m, 2H), 2.60 (s, 3H), 2.56 (br.s, 2H), 2.38 (s, 3H), 1.88 (dq, $J=12.7$, 6.4 Hz, 1H), 1.54 (d, $J=5.3$ Hz, 2H), 1.34 (s, 3H), 1.04 (d, $J=6.8$ Hz, 3H), 1.02 (d, $J=6.5$ Hz, 3H); LCMS (ESI) m/e 387.1 $[(M+H)^+]$, calcd $C_{21}H_{31}N_4O_3$, 387.2]; LC/MS retention time (method B): $t_R = 1.54$ min.

15

Example 214

(*S*)-2,4-dimethyl-1-(4-(quinazolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine



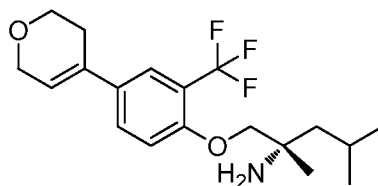
Prepared as described in Example 19. Obtained (*S*)-2,4-dimethyl-1-(4-(quinazolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (8.5 mg, 0.020 mmol, 19% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.34 (s, 1H), 8.17 - 8.03 (m, 5H), 7.79 (t, $J=7.5$ Hz, 1H), 7.47 (d, $J=8.4$ Hz, 1H), 3.94 (d, $J=7.3$ Hz, 2H), 1.85 - 1.76 (m, 1H), 1.43 (m, 2H), 1.16 (s, 3H), 0.97 - 0.89 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 404.2 $[(M+H)^+]$, calcd $C_{22}H_{25}F_3N_3O$, 404.4]; LC/MS retention time (method B): $t_R = 2.01$ min.

20

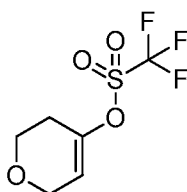
25

Example 215

(*S*)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



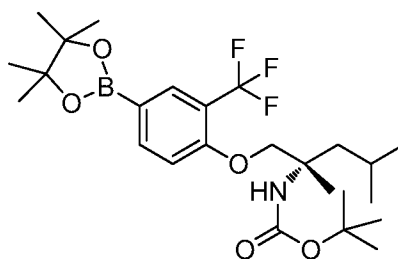
5



Part A: 3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonate

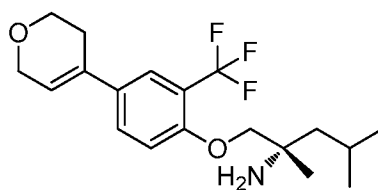
KHMDS (6.66 mL, 3.33 mmol) was added to the THF (7 mL) solution of dihydro-2H-pyran-4(3H)-one (0.2224 g, 2.221 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (0.952 g, 2.67 mmol) at -78 °C. The reaction was stirred for 30 min. The reaction was diluted with diethyl ether and washed with water (3x). The diethyl ether layer was separated, dried (Na₂SO₄), filtered and concentrated. The crude material was carried on without further purification.

15



Part B: (S)-tert-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate

Prepared as described in Example 77, Part C. The crude material was carried on without further purification. LCMS (ESI) *m/e* 523.2 [(M+Na)⁺, calcd C₂₅H₃₉BF₃NO₅Na, 524.3]; LC/MS retention time (method B): *t*_R = 2.61 min.

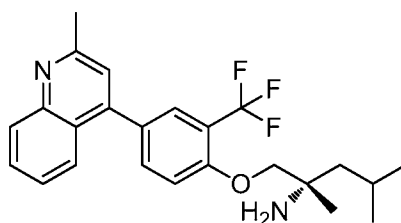


Part C: (S)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

A mixture of 2N sodium carbonate solution (0.106 mL, 0.212 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (6.06 mg, 7.42 μ mol), 3,6-dihydro-2H-pyran-4-yl trifluoromethanesulfonate (98 mg, 0.424 mmol) and (S)-tert-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (53.1 mg, 0.106 mmol) in dioxane (2 mL) (degassed) was heated at 120 °C for 5 h. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was diluted with DCM (3 mL) and TFA (2 mL, 26.0 mmol) was added at room temperature. The reaction was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure and the residue was purified by reverse phase Prep HPLC to give (S)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (2.7 mg, 0.213 mmol, 7% yield over three steps). ¹H NMR (500MHz, DMSO-d₆) δ 7.69 (d, *J*=8.4 Hz, 1H), 7.61 (s, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 6.24 (m, 1H), 4.21 (d, *J*=2.6 Hz, 2H), 3.83 - 3.79 (m, 4H), 2.42 (br. s., 2H), 1.80 - 1.72 (m, 1H), 1.42 - 1.37 (m, 2H), 1.12 (s, 3H), 0.89 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 358.3 [(M+H)⁺, calcd C₁₉H₂₇F₃NO₂, 358.2]; LC/MS retention time (method B): *t*_R = 1.99 min.

Example 216

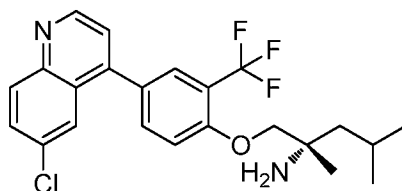
(S)-2,4-dimethyl-1-(4-(2-methylquinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine



A mixture of 2N sodium carbonate solution (0.157 mL, 0.314 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (8.97 mg, 10.99 μ mol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.079 g, 0.157mmol) (prepared in Example 215, Part B) and 4-chloro-2-methylquinoline (0.05 mL, 0.248 mmol) in dioxane (1 mL) (degassed) was heated at 120 °C for 5 h. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was diluted with DCM (3 mL) and was added TFA (2 mL, 26.0 mmol) at room temperature. The reaction was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure and the material was purified by reverse phase HPLC/MS to afford (*S*)-2,4-dimethyl-1-(4-(2-methylquinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (14.8 mg, 0.035 mmol, 22% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.02 (d, *J*=8.4 Hz, 1H), 7.83 - 7.73 (m, 4H), 7.55 (t, *J*=7.5 Hz, 1H), 7.44 - 7.41 (m, 2H), 3.94 - 3.87 (m, 2H), 3.47 (br. s., 2H), 2.70 (s, 3H), 1.87 - 1.79 (m, 1H), 1.42 (d, *J*=5.5 Hz, 2H), 1.15 (s, 3H), 0.95 (d, *J*=2.9 Hz, 3H), 0.93 (d, *J*=2.9 Hz, 3H); LCMS (ESI) *m/e* 417.3 [(M+H)⁺, calcd C₂₄H₂₈F₃N₂O, 417.2]; LC/MS retention time (method B): *t_R* = 2.26 min.

Example 217

(*S*)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

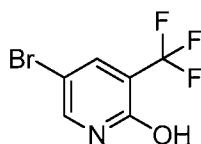
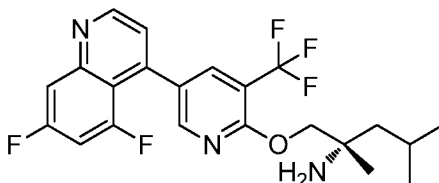


Preparation was described as Example 19. Intermediate 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline was prepared as described in Example 77, Part B and Part C. Obtained (*S*)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (3.9 mg, 8.66 μ mol, 7% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.98 (d, *J*=4.4 Hz, 1H), 8.16 (d, *J*=8.8 Hz, 1H), 7.85 (dd, *J*=9.0, 2.4 Hz, 2H), 7.79 (d, *J*=2.6 Hz, 2H), 7.59 (d, *J*=4.4 Hz, 1H), 7.45 (d, *J*=8.8 Hz, 1H), 3.97 - 3.89 (m, 2H), 1.83 (dt, *J*=12.7, 6.1 Hz, 1H), 1.43 (d,

$J=4.8$ Hz, 2H), 1.16 (s, 3H), 0.94 (m, 6H); LCMS (ESI) m/e 419.9 $[(M-NH_2)^+]$, calcd $C_{23}H_{22}ClF_3NO$, 420.1]; LC/MS retention time (method B): $t_R = 2.07$ min.

Example 218

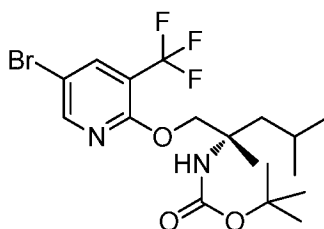
5 *(S)*-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



10 *Part A: 5-Bromo-3-(trifluoromethyl)pyridin-2-ol*

NBS (2.334 g, 13.11 mmol) was added portionwise to a solution of 3-(trifluoromethyl)pyridin-2-ol (1.6449 g, 10.09 mmol) in THF (15 mL) at room temperature. The reaction was stirred at room temperature over the weekend. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give crude 5-bromo-3-(trifluoromethyl)pyridin-2-ol (2.12 g, 6.57 mmol, 65% yield) as a yellow solid. The material was carried on without further purification. LCMS (ESI) m/e 241.8 $[(M+H)^+]$, calcd $C_6H_4BrF_3NO$, 241.9]; LC/MS retention time (method B): $t_R = 1.57$ min.

20



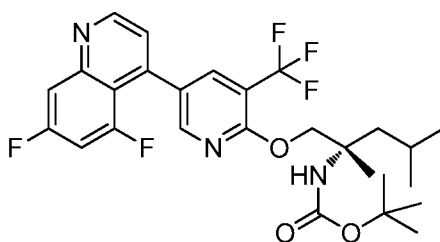
Part B: (S)-tert-butyl 1-((5-bromo-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl carbamate

A mixture of potassium carbonate (0.113 g, 0.814 mmol), *(S)*-tert-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.1593 g, 0.543

mmol) and 5-bromo-3-(trifluoromethyl)pyridin-2-ol (0.197 g, 0.814 mmol) in DMF (2 mL) was heated at 80 °C overnight. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was separated, dried (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was

5 purified by silica gel chromatography (eluted with ethyl acetate in hexane from 0 to 10%) to give (*S*)-*tert*-butyl (1-((5-bromo-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.059 g, 0.111 mmol, 20% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.34 (d, *J*=2.5 Hz, 1H), 7.95 (d, *J*=2.5 Hz, 1H), 4.59 - 4.52 (m, 2H), 4.39 (d, *J*=10.3 Hz, 1H), 1.89 - 1.72 (m, 2H), 1.54 (d, *J*=8.8 Hz,

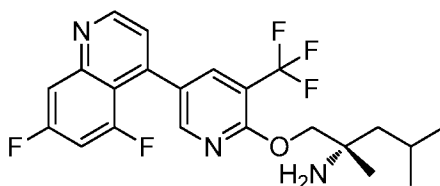
10 1H), 1.39 (s, 9H), 1.37 (s, 3H), 0.97 (m, 6H); ¹⁹F NMR (376MHz, CHLOROFORM-*d*) δ -64.11 (s, 3F). LCMS (ESI) *m/e* 476.9 [(M+Na)⁺, calcd C₁₈H₂₆BrF₃N₂O₃Na, 477.1]; LC/MS retention time (method B): *t*_R = 2.54 min.



15 *Part C: (S)-tert-butyl (1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Prepared as described in Example 193. Obtained (*S*)-*tert*-butyl (1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (26.0 mg, 0.048 mmol, 80% yield). LCMS (ESI) *m/e* 540.2 [(M+H)⁺,

20 calcd C₂₇H₃₁F₅N₃O₃, 540.2]; LC/MS retention time (method B): *t*_R = 2.53 min.



Part D: (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

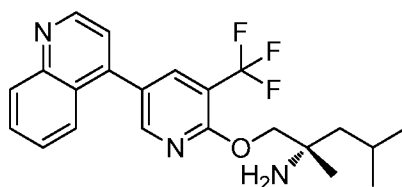
25 TFA deprotection was performed as described in Example 32. Obtained (*S*)-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-

dimethylpentan-2-amine (12.5 mg, 0.025 mmol, 56% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.34 (s, 1H), 8.17 - 8.03 (m, 5H), 7.79 (t, $J=7.5$ Hz, 1H), 7.47 (d, $J=8.4$ Hz, 1H), 3.94 (d, $J=7.3$ Hz, 2H), 1.85 - 1.76 (m, 1H), 1.43 (m, 2H), 1.16 (s, 3H), 0.97 - 0.89 (m, 6H). LCMS (ESI) m/e 440.1 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{22}\text{H}_{23}\text{F}_5\text{N}_3\text{O}$, 440.2];

5 LC/MS retention time (method B): $t_R = 2.04$ min.

Example 219

(*S*)-2,4-dimethyl-1-((5-(quinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)pentan-2-amine



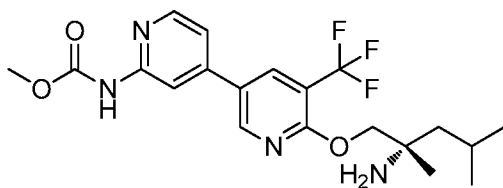
10

Prepared as described in Example 218. Obtained (*S*)-2,4-dimethyl-1-((5-(quinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)pentan-2-amine (6.1 mg, 0.015 mmol, 60% yield) as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 8.99 (d, $J=4.4$ Hz, 1H), 8.63 (s, 1H), 8.31 (s, 1H), 8.14 (d, $J=8.4$ Hz, 1H), 7.88 - 7.82 (m, 2H), 7.66 (t, $J=7.5$ Hz, 1H), 7.60 (d, $J=4.4$ Hz, 1H), 4.25 - 4.18 (m, 2H), 1.84 (dt, $J=12.7, 6.1$ Hz, 1H), 1.42 (d, $J=5.5$ Hz, 2H), 1.15 (s, 3H), 0.94 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 404.0 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{22}\text{H}_{25}\text{F}_3\text{N}_3\text{O}$, 404.4]; LC/MS retention time (method B): $t_R = 1.77$ min.

15

Example 220

(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate



20

Prepared as described in Example 218. Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate (13.8 mg, 0.032 mmol, 96% yield) as an off-white solid. ^1H NMR (500MHz, DMSO- d_6) δ 10.35 (br. s., 1H), 8.79 (s, 1H), 8.38 - 8.32 (m, 2H), 8.11 (s, 1H), 7.48 (d, $J=5.1$ Hz,

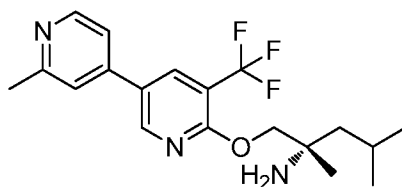
25

1H), 4.17 (q, $J=10.3$ Hz, 2H), 3.38 (br. s., 3H), 1.85 - 1.74 (m, 1H), 1.38 (d, $J=5.5$ Hz, 2H), 1.11 (s, 3H), 0.91 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 427.0 $[(M+H)^+]$, calcd $C_{20}H_{26}F_3N_4O_3$, 427.2]; LC/MS retention time (method B): $t_R = 1.84$ min.

5

Example 221

(*S*)-2,4-dimethyl-1-((2'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)pentan-2-amine

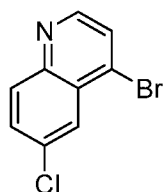
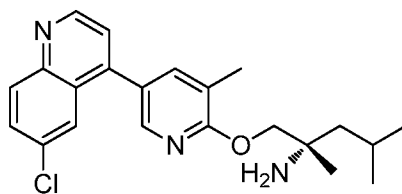


10 Prepared as described in Example 218. Obtained (*S*)-2,4-dimethyl-1-((2'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)pentan-2-amine (4.6 mg, 0.012 mmol, 68% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.87 (s, 1H), 8.52 (d, $J=5.1$ Hz, 1H), 8.46 (s, 1H), 7.72 (s, 1H), 7.62 (d, $J=4.0$ Hz, 1H), 4.16 (q, $J=10.1$ Hz, 2H), 2.54 (s, 3H), 1.84 - 1.75 (m, 1H), 1.37 (d, $J=5.5$ Hz, 2H), 1.10 (s, 3H), 0.91 (m, 6H), two
15 exchangeable protons not observed; LCMS (ESI) m/e 368.0 $[(M+H)^+]$, calcd $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): $t_R = 1.57$ min.

Example 222

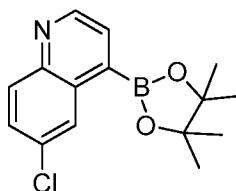
(*S*)-1-((5-(6-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

20

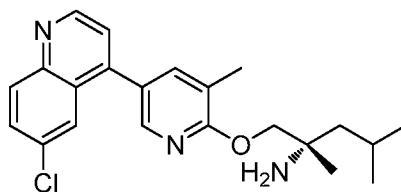


Part A: 4-Bromo-6-chloroquinoline

Prepared as described in Example 77, Part B. Obtained 4-Bromo-6-chloroquinoline (0.322 g, 1.33 mmol, 76% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.68 (d, *J*=4.8 Hz, 1H), 8.21 (d, *J*=2.3 Hz, 1H), 8.07 (d, *J*=8.8 Hz, 1H), 7.76 - 7.70 (m, 2H). LCMS (ESI) *m/e* 243.7 [(M+H)⁺, calcd C₉H₅BrNCl, 243.5]; LC/MS retention time (method B): *t*_R = 2.07 min.

*Part B: 7-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline*

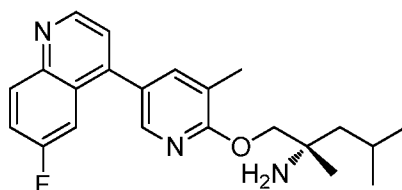
Prepared as described in Example 77, Part C. Carried on without further purification. LCMS (ESI) *m/e* 207.9 [(M-NH₂)⁺, calcd C₉H₇BNCIO₂, 207.0]; LC/MS retention time (method B): *t*_R = 1.21 min.

*Part C: (S)-1-((5-(6-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine*

Intermediate (S)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine prepared as in Example 52, Part A. Suzuki reaction was performed as described in Example 193. Obtained (S)-1-((5-(6-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (56.7 mg, 0.143 mmol, 26% yield over two steps). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.94 (d, *J*=4.5 Hz, 1H), 8.14 (d, *J*=9.0 Hz, 1H), 8.08 (d, *J*=1.8 Hz, 1H), 7.82 (d, *J*=2.3 Hz, 1H), 7.69 (dd, *J*=8.8, 2.3 Hz, 1H), 7.57 - 7.54 (m, 1H), 7.32 (d, *J*=4.5 Hz, 1H), 4.64 - 4.42 (m, 2H), 1.93 - 1.75 (m, 3H), 1.54 (s, 3H), 1.03 (d, *J*=6.3 Hz, 3H), 1.01 (d, *J*=6.3 Hz, 3H), two exchangeable protons not observed; LCMS (ESI) *m/e* 366.9 [(M-NH₂)⁺, calcd C₂₂H₂₄N₂ClO, 367.2]; LC/MS retention time (method B): *t*_R = 1.88 min.

Example 223

(*S*)-1-((5-(6-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



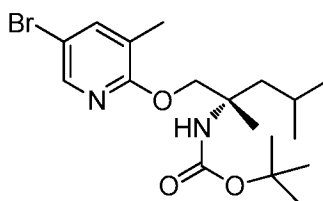
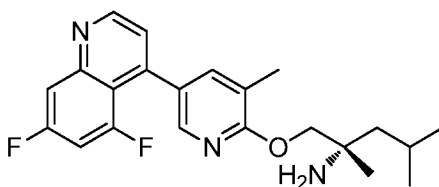
5

Intermediate (*S*)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine prepared as described in Example 52, Part A. The corresponding borolate was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((5-(6-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (9.7 mg, 0.026 mmol, 14% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.92 (d, *J*=4.5 Hz, 1H), 8.31 - 8.16 (m, 1H), 8.12 (d, *J*=2.0 Hz, 1H), 7.61 - 7.49 (m, 3H), 7.34 (d, *J*=4.3 Hz, 1H), 4.27 - 4.18 (m, 2H), 2.35 (s, 3H), 1.93 - 1.78 (m, 1H), 1.63 - 1.49 (m, 2H), 1.29 (s, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.01 (d, *J*=6.8 Hz, 3H), two exchangeable protons not observed; LCMS (ESI) *m/e* 368.2 [(*M*+H)⁺, calcd C₂₂H₂₇N₃FO, 368.2]; LC/MS retention time (method B): *t*_R = 1.78 min.

Example 224

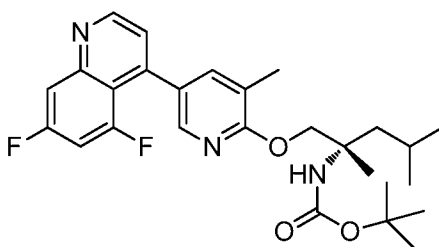
(*S*)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

20



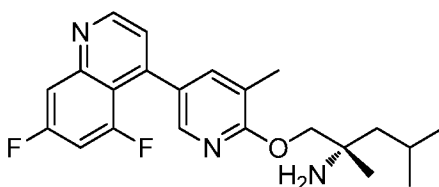
Part A: (S)-tert-butyl (1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 53, Part A. obtained (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (3.06 g, 7.32 mmol, 86% yield). LCMS (ESI) m/e 422.9 [(M+Na)⁺, calcd C₁₈H₂₉BrN₂O₃Na, 423.1]; LC/MS retention time (method B): t_R = 2.48 min.



Part B: (S)-tert-butyl (1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki reaction was performed as described in Example 193. Obtained (S)-tert-butyl (1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (43.8 mg, 0.090 mmol, 59% yield). LCMS (ESI) m/e 486.1 [(M+H)⁺, calcd C₂₇H₃₄N₃F₂O₃, 486.3]; LC/MS retention time (method B): t_R = 2.44 min.



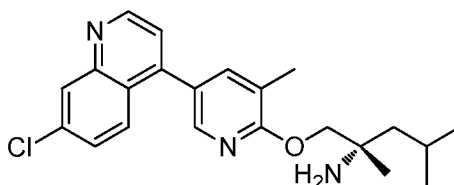
Part C: (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection was performed as described in Example 32. Obtained (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (33.9 mg, 0.088 mmol, 98% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.00 (d, J =4.4 Hz, 1H), 8.10 (s, 1H), 7.79 (d, J =9.5 Hz, 1H), 7.75 (br. s., 1H), 7.61 - 7.52 (m, 1H), 7.45 (d, J =4.4 Hz, 1H), 4.45 - 4.31 (m, 2H), 2.33 (s, 3H), 1.89 - 1.74 (m, 2H), 1.66 (dd, J =14.1, 5.3 Hz, 1H), 1.42 (s, 3H), 0.98 (d, J =6.6 Hz, 3H), 0.94 (d, J =6.6

Hz, 3H), two exchangeable protons not observed; LCMS (ESI) m/e 386.3 $[(M+H)^+]$, calcd $C_{22}H_{26}N_3F_2O$, 386.2]; LC/MS retention time (method B): t_R = 1.84 min.

Example 225

5 (S)-1-((5-(7-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

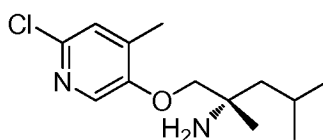
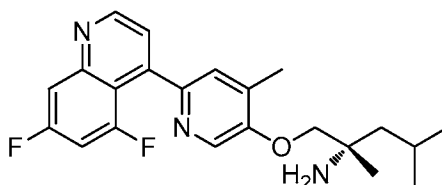


Intermediate (S)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine was prepared as described in Example 52, Part A. The corresponding
 10 borolate was prepared as described in Example 77, Part C. Suzuki reaction was performed as described in Example 193. Obtained (S)-1-((5-(7-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (22.5 mg, 0.058 mmol, 51% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.98 (d, J =4.4 Hz, 1H), 8.17 (s, 2H), 7.96 - 7.91 (m, 1H), 7.81 (s, 1H), 7.66 (dd, J =9.0, 2.0 Hz, 1H), 7.53 (d, J =4.4 Hz, 1H), 4.15
 15 - 4.07 (m, 2H), 2.30 (s, 3H), 1.87 - 1.79 (m, 1H), 1.45 (t, J =6.4 Hz, 2H), 1.17 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 384.3 $[(M+H)^+]$, calcd $C_{22}H_{27}N_3ClO$, 384.2]; LC/MS retention time (method B): t_R = 1.98 min.

20

Example 226

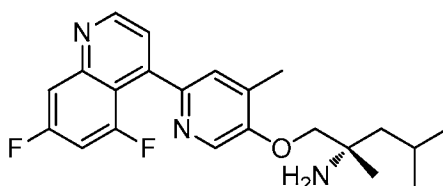
(S)-1-((6-(5,7-difluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



25

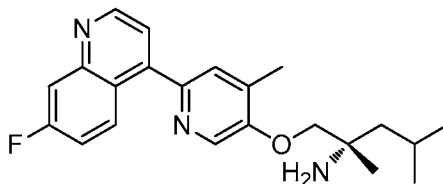
Part A: (S)-1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

A mixture of TFA (0.4 mL, 5.19 mmol) and (*S*)-*tert*-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.064 g, 0.179 mmol, 0.179 mmol) in CH₂Cl₂ (4 mL) was stirred at room temperature for 4 h. LCMS showed complete conversion to (*S*)-1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine. The solvent was removed via vacuum and the material was used without further purification. LCMS (ESI) *m/e* 257.1 [(M+H)⁺, calcd C₁₃H₂₂ClN₂O, 257.1]; LC/MS retention time (method B): *t*_R = 1.64 min.

*Part B: (S)-1-((6-(5,7-difluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine*

Suzuki coupling was performed as described in Example 77, Part D. Obtained (*S*)-1-((6-(5,7-difluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (12.2 mg, 0.031 mmol, 43% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.01 (d, *J*=4.4 Hz, 1H), 8.30 (s, 1H), 7.78 (d, *J*=8.8 Hz, 1H), 7.53 (br. s., 1H), 7.49 (d, *J*=4.4 Hz, 1H), 7.47 (s, 1H), 3.94 (s, 2H), 2.31 (s, 3H), 1.88 - 1.80 (m, 1H), 1.48 (dd, *J*=13.0, 5.3 Hz, 2H), 1.20 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 386.0 [(M+H)⁺, calcd C₂₂H₂₆F₂N₃O, 386.2]; LC/MS retention time (method B): *t*_R = 1.79 min.

Example 227

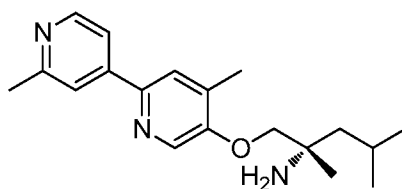
(S)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as described in Example 226. Obtained (*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (6.0 mg, 0.016 mmol,

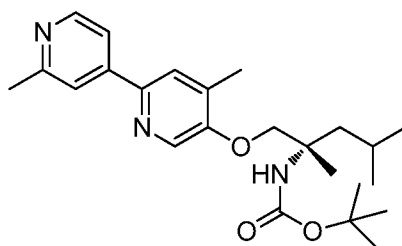
63% yield). ^1H NMR (400MHz, DMSO- d_6) δ 8.98 (d, $J=4.5$ Hz, 1H), 8.47 (s, 1H), 8.34 (dd, $J=9.3$, 6.3 Hz, 1H), 7.82 (dd, $J=10.3$, 2.8 Hz, 1H), 7.67 (s, 1H), 7.59 (d, $J=4.5$ Hz, 1H), 7.55 (td, $J=8.9$, 2.8 Hz, 1H), 4.10 (s, 2H), 2.37 (s, 3H), 1.86 - 1.78 (m, 1H), 1.63 (br. s., 1H), 1.57 - 1.50 (m, 1H), 1.30 (s, 3H), 0.95 (dd, $J=11.7$, 6.7 Hz, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 368.0 $[(M+H)^+]$, calcd $\text{C}_{22}\text{H}_{27}\text{FN}_3\text{O}$, 368.2]; LC/MS retention time (method B): $t_R = 1.67$ min.

Example 228

(*S*)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

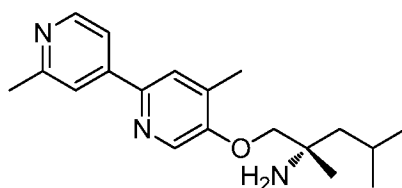


10



Part A: (S)-tert-butyl (1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

15 Suzuki coupling was performed as described in Example 77, Part D. The crude was used in the next reaction without purification. LCMS (ESI) m/e 414.0 $[(M+H)^+]$, calcd $\text{C}_{24}\text{H}_{36}\text{N}_3\text{O}_3$, 414.3]; LC/MS retention time (method B): $t_R = 2.02$ min.



20

Part B: (S)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

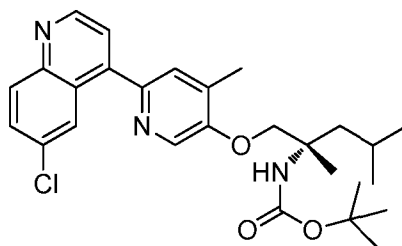
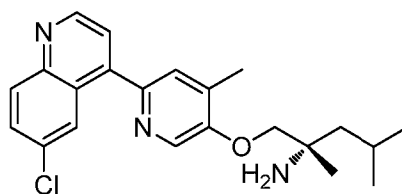
TFA deprotection as described in Example 32. Obtained (*S*)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (2.2 mg, 6.95 μmol ,

17% yield over two steps). ^1H NMR (600MHz, DMSO- d_6) δ 8.50 (d, $J=5.1$ Hz, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.78 (d, $J=5.1$ Hz, 1H), 3.88 (br. s., 2H), 2.54 (s, 3H), 2.31 (s, 3H), 1.82 (br. s., 1H), 1.45 - 1.38 (m, 2H), 1.15 (s, 3H), 0.93 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 314.1 $[(\text{M}+\text{H})^+]$,
 5 calcd $\text{C}_{19}\text{H}_{28}\text{N}_3\text{O}$, 314.2]; LC/MS retention time (method B): t_R = 1.50 min.

Example 229

(*S*)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

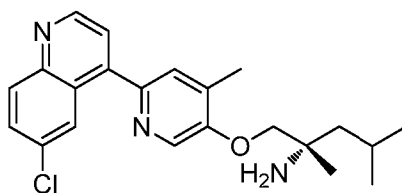
10



Part A: (*S*)-tert-butyl (1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

15 Suzuki coupling was performed as described in Example 77, Part D. The crude was used in the next reaction without purification. LCMS (ESI) m/e 483.9 $[(\text{M}+\text{H})^+]$, calcd $\text{C}_{27}\text{H}_{35}\text{ClN}_3\text{O}_3$, 484.2]; LC/MS retention time (method B): t_R = 2.24 min.

20

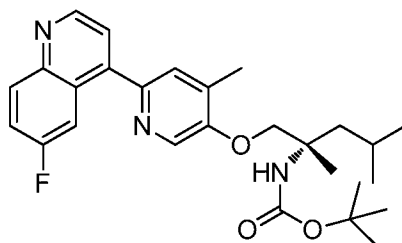
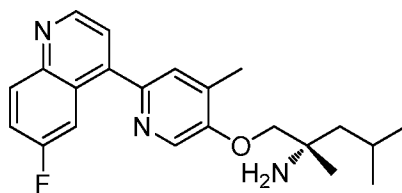


Part B: (S)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (S)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (6.8 mg, 0.017 mmol, 16% yield over two steps). ¹H NMR (500MHz, DMSO-d₆) δ 9.00 (d, *J*=4.4 Hz, 1H), 8.48 (s, 1H), 8.40 (d, *J*=2.2 Hz, 1H), 8.12 (d, *J*=9.2 Hz, 1H), 7.82 (dd, *J*=8.8, 2.2 Hz, 1H), 7.71 (s, 1H), 7.69 (d, *J*=4.8 Hz, 1H), 3.95 (s, 2H), 2.35 (s, 3H), 1.84 (d, *J*=6.2 Hz, 1H), 1.45 (t, *J*=6.6 Hz, 2H), 1.18 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 383.9 [(M+H)⁺, calcd C₂₂H₂₇ClN₃O, 384.2]; LC/MS retention time (method B): *t_R* = 1.81 min.

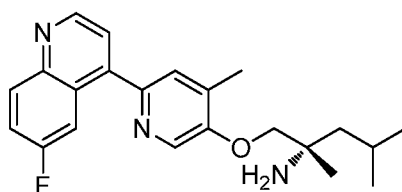
Example 230

(S)-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-tert-butyl (1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D. Obtained (S)-tert-butyl (1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (33.2 mg, 0.035 mmol, 35% yield). LCMS (ESI) *m/e* 468.2 [(M+H)⁺, calcd C₂₇H₃₅FN₃O₃, 468.3]; LC/MS retention time (method B): *t_R* = 2.22 min.

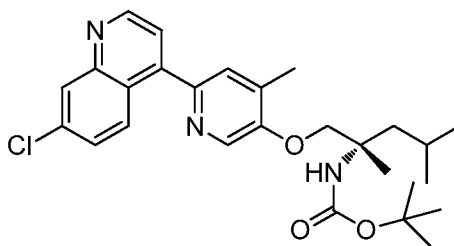
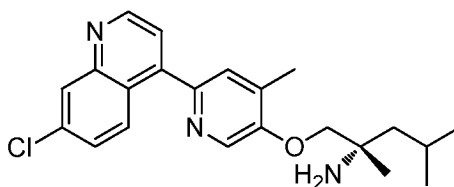


Part B: *(S)*-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained *(S)*-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (21.7 mg, 0.058 mmol, 82% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.98 (d, $J=4.4$ Hz, 1H), 8.53 (s, 1H), 8.18 (dd, $J=9.2, 5.5$ Hz, 1H), 8.07 (dd, $J=11.0, 2.9$ Hz, 1H), 7.73 (s, 2H), 7.69 (d, $J=4.4$ Hz, 1H), 4.15 (d, $J=4.4$ Hz, 2H), 2.39 (s, 3H), 1.89 - 1.81 (m, 1H), 1.66 (d, $J=5.1$ Hz, 1H), 1.56 (dd, $J=14.1, 5.3$ Hz, 1H), 1.33 (s, 3H), 0.99 (d, $J=6.6$ Hz, 3H), 0.96 (d, $J=6.6$ Hz, 3H), two exchangeable protons not observed; LCMS (ESI) m/e 368.2 $[(M+H)^+]$, calcd $\text{C}_{22}\text{H}_{27}\text{FN}_3\text{O}$, 368.2; LC/MS retention time (method B): t_R = 1.67 min.

Example 231

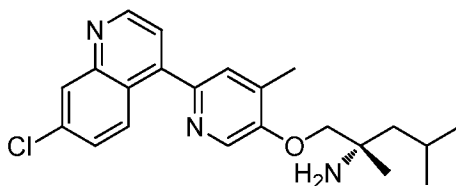
(S)-1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: *(S)*-tert-butyl (1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D. The crude was used in the next reaction without purification. LCMS (ESI) m/e 484.2

$[(M+H)^+]$, calcd $C_{27}H_{35}ClN_3O_3$, 484.2]; LC/MS retention time (method B): $t_R = 2.32$ min.



5

Part B: (S)-1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

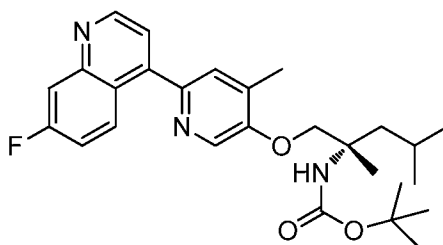
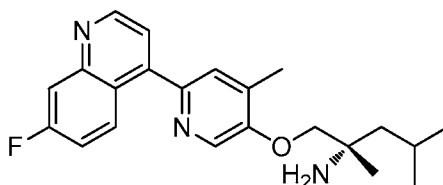
TFA deprotection as described in Example 32. Obtained (*S*)-*tert*-butyl (1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (15.5 mg, 0.039 mmol, 34% yield over two steps). ^1H NMR (500MHz, DMSO- d_6) δ 8.98 (d, $J=4.4$ Hz, 1H), 8.53 (s, 1H), 8.18 (dd, $J=9.2, 5.5$ Hz, 1H), 8.07 (dd, $J=11.0, 2.9$ Hz, 1H), 7.73 (s, 2H), 7.69 (d, $J=4.4$ Hz, 1H), 4.15 (d, $J=4.4$ Hz, 2H), 2.39 (s, 3H), 1.89 - 1.81 (m, 1H), 1.66 (d, $J=5.1$ Hz, 1H), 1.56 (dd, $J=14.1, 5.3$ Hz, 1H), 1.33 (s, 3H), 0.99 (d, $J=6.6$ Hz, 3H), 0.96 (d, $J=6.6$ Hz, 3H), two exchangeable protons not observed; LCMS (ESI) m/e 384.1 $[(M+H)^+]$, calcd $C_{22}H_{27}ClN_3O$, 384.2]; LC/MS retention time (method B): $t_R = 1.84$ min.

15

Example 232

(*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

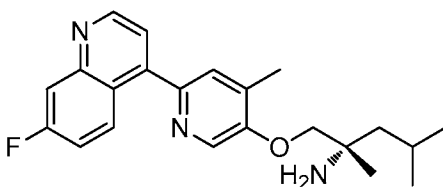
20



Part A: (*S*)-*tert*-butyl (1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

Obtained (*S*)-*tert*-butyl (1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (56 mg, 0.055 mmol, 27% yield). LCMS (ESI) *m/e* 468.0 [(M+H)⁺, calcd C₂₇H₃₅FN₃O₃, 468.3]; LC/MS retention time (method B): *t*_R = 2.24 min.



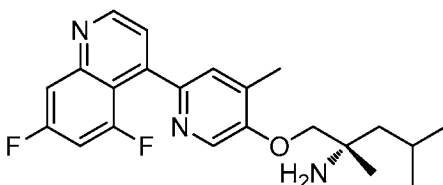
Part B: (*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (36.4 mg, 0.095 mmol, 89% yield). ¹H NMR (400MHz, DMSO-d₆) δ 8.98 (d, *J*=4.5 Hz, 1H), 8.47 (s, 1H), 8.34 (dd, *J*=9.3, 6.3 Hz, 1H), 7.82 (dd, *J*=10.3, 2.8 Hz, 1H), 7.67 (s, 1H), 7.59 (d, *J*=4.5 Hz, 1H), 7.55 (td, *J*=8.9, 2.8 Hz, 1H), 4.10 (s, 2H), 2.37 (s, 3H), 1.86 - 1.78 (m, 1H), 1.63 (br. s., 1H), 1.57 - 1.50 (m, 1H), 1.30 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 368.0 [(M+H)⁺, calcd C₂₂H₂₇FN₃O, 368.2]; LC/MS retention time (method B): *t*_R = 1.67 min.

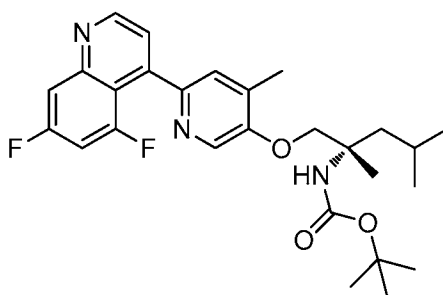
20

Example 233

(*S*)-1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



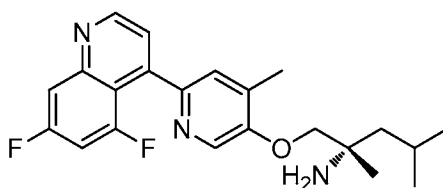
25



Part A: (*S*)-tert-butyl (1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

- 5 Obtained (*S*)-tert-butyl (1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (50.6 mg, 0.062 mmol, 62% yield). LCMS (ESI) m/e 506.2 $[(M+H)^+]$, calcd $C_{26}H_{31}ClF_2N_3O_3$, 506.2]; LC/MS retention time (method B): t_R = 2.43 min.



10

Part B: (*S*)-1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

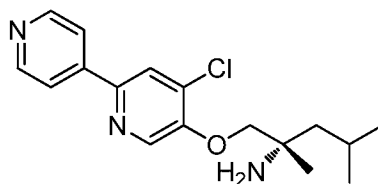
- TFA deprotection as described in Example 32. Obtained (*S*)-1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (16.2 mg, 0.040 mmol, 40% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.04 (d, J =4.4 Hz, 1H), 8.55 (s, 1H), 7.88 (s, 1H), 7.81 (d, J =9.5 Hz, 1H), 7.61 - 7.53 (m, 2H), 4.04 (s, 2H), 1.88 - 1.77 (m, 1H), 1.52 - 1.40 (m, 2H), 1.20 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 406.1 $[(M+H)^+]$, calcd $C_{21}H_{23}ClF_2N_3O$, 406.1]; LC/MS retention time (method A): t_R = 1.82 min.

20

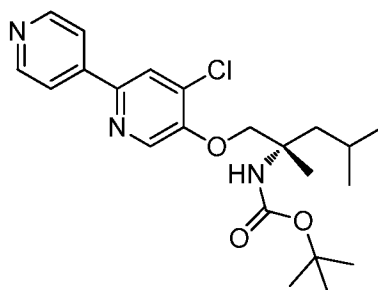
25

Example 234

(S)-1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



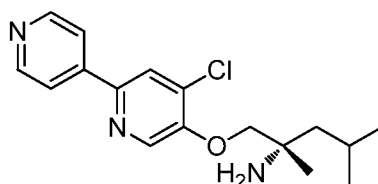
5



Part A: (S)-tert-butyl (1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

10 Suzuki coupling was performed as described in Example 77, Part D. Obtained (S)-tert-butyl (1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (24.6 mg, 0.059 mmol, 25% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.72 (br. s., 2H), 8.41 (s, 1H), 7.83 (s, 3H), 4.59 (s, 1H), 4.41 (d, *J*=8.8 Hz, 1H), 4.21 (d, *J*=8.8 Hz, 1H), 1.95 - 1.80 (m, 2H), 1.56 (dd, *J*=13.9, 4.9

15 Hz, 1H), 1.44 (s, 3H), 1.40 (s, 9H), 1.01 (m, 6H). LCMS (ESI) *m/e* 420.2 [(M+H)⁺, calcd C₂₂H₃₁ClN₃O₃, 420.2]; LC/MS retention time (method A): *t_R* = 2.07 min.



Part B: (S)-1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

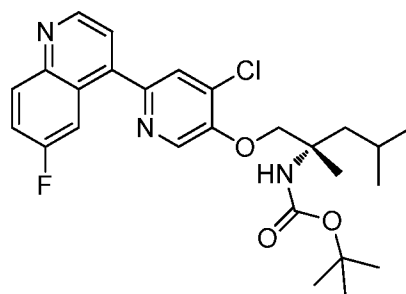
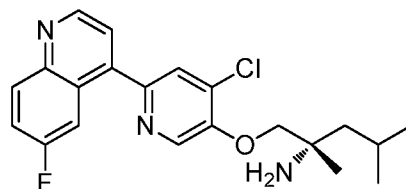
20 TFA deprotection as described in Example 32. Obtained (S)-1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (7.2 mg, 0.022 mmol, 96% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.68 (d, *J*=5.9 Hz, 2H), 8.64 (s, 1H), 8.35 (s, 1H), 8.04 (d, *J*=5.9 Hz, 2H), 4.18 (s, 2H), 1.85 - 1.77 (m, 1H), 1.66 - 1.60 (m,

1H), 1.52 (dd, $J=14.1, 5.3$ Hz, 1H), 1.29 (s, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 0.93 (d, $J=6.6$ Hz, 3H); LCMS (ESI) m/e 303.1 $[(M-NH_2)^+]$, calcd $C_{17}H_{20}ClN_2O$, 303.1]; LC/MS retention time (method B): $t_R = 1.44$ min.

5

Example 235

(*S*)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



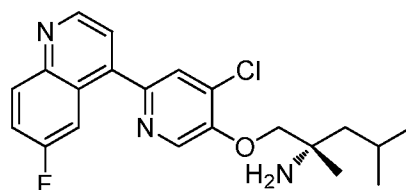
10

Part A: (*S*)-tert-butyl (1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

Obtained (*S*)-tert-butyl (1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (62.0 mg, 0.109 mmol, 45% yield). LCMS (ESI) m/e 488.2 $[(M+H)^+]$, calcd $C_{26}H_{32}ClFN_3O_3$, 488.2]; LC/MS retention time (method B): $t_R = 2.37$ min.

15



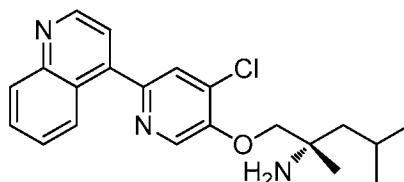
20

Part B: (S)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (S)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (42.3 mg, 0.109 mmol, 86% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.99 (d, *J*=4.4 Hz, 1H), 8.76 (s, 1H), 8.19 (dd, *J*=9.2, 5.9 Hz, 1H), 8.07 (s, 1H), 8.03 (dd, *J*=11.0, 2.9 Hz, 1H), 7.77 - 7.71 (m, 2H), 4.30 (s, 2H), 1.86 (dt, *J*=12.5, 6.2 Hz, 1H), 1.77 - 1.69 (m, 1H), 1.60 (dd, *J*=14.1, 5.7 Hz, 1H), 1.37 (s, 3H), 0.97 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 388.1 [(M+H)⁺, calcd C₂₁H₂₄ClFN₃O, 388.2]; LC/MS retention time (method B): *t*_R = 1.75 min.

Example 236

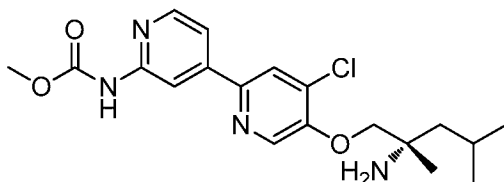
(S)-1-((4-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 233. Obtained (S)-1-((4-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (2.6 mg, 6.82 μmol, 16% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.00 (d, *J*=4.4 Hz, 1H), 8.70 (s, 1H), 8.21 (d, *J*=8.4 Hz, 1H), 8.12 (d, *J*=8.4 Hz, 1H), 8.00 (s, 1H), 7.82 (t, *J*=7.3 Hz, 1H), 7.69 - 7.56 (m, 2H), 4.09 (s, 2H), 1.86 (dt, *J*=13.0, 6.3 Hz, 1H), 1.49 (qd, *J*=13.9, 5.5 Hz, 2H), 1.22 (s, 3H), 0.96 (t, *J*=6.8 Hz, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 370.0 [(M+H)⁺, calcd C₂₁H₂₅ClN₃O, 370.2]; LC/MS retention time (method B): *t*_R = 1.75 min.

Example 237

(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-chloro-[2,4'-bipyridin]-2'-yl)carbamate



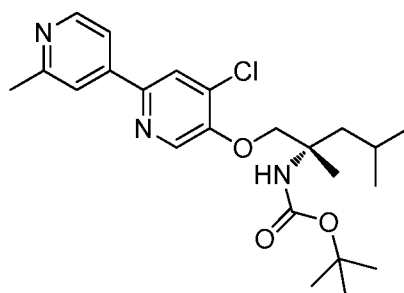
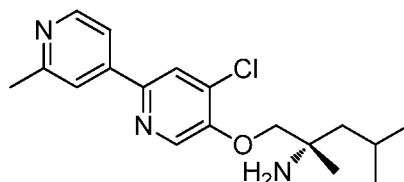
Suzuki coupling was performed as described in Example 77, Part D.

Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-chloro-[2,4'-bipyridin]-2'-yl)carbamate (8.1 mg, 0.020 mmol, 35% yield). ¹H NMR (600MHz, DMSO-d₆) δ 8.59 (s, 1H), 8.52 (s, 1H), 8.34 (d, *J*=5.5 Hz, 1H), 8.19 (s, 1H), 7.67 (d, *J*=5.5 Hz, 1H), 4.01 - 3.96 (m, 2H), 3.71 (s, 3H), 1.85 - 1.77 (m, 1H), 1.45 - 1.36 (m, 2H), 1.17 - 1.12 (m, 3H), 0.95 - 0.89 (m, 6H), three exchangeable protons not observed; LCMS (ESI) *m/e* 393.0 [(M+H)⁺, calcd C₁₉H₂₆ClN₄O₃, 393.2]; LC/MS retention time (method B): *t*_R = 1.63 min.

10

Example 238

(*S*)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

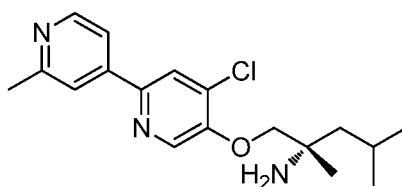


15 *Part A: (S)-tert-butyl (1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate*

Suzuki coupling was performed as described in Example 77, Part D.

Obtained (*S*)-tert-butyl (1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (107.4 mg, 0.247 mmol, 49% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.57 (d, *J*=5.0 Hz, 1H), 8.38 (s, 1H), 7.80 (s, 1H), 7.70 (d, *J*=0.5 Hz, 1H), 7.59 (dd, *J*=5.3, 1.3 Hz, 1H), 4.39 (d, *J*=8.5 Hz, 1H), 4.19 (d, *J*=8.8 Hz, 1H), 2.64 (s, 3H), 1.95 - 1.77 (m, 2H), 1.55 (dd, *J*=13.9, 4.9 Hz, 1H), 1.43 (s, 3H), 1.39 (s, 9H), 1.00 (m, 6H), one exchangeable proton not observed; LCMS (ESI) *m/e* 434.2 [(M+H)⁺, calcd C₂₃H₃₃ClN₃O₃, 433.2]; LC/MS retention time (method B): *t*_R = 2.07 min.

25

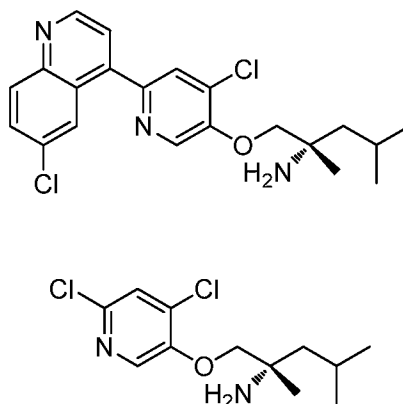


Part B: (S)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (S)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (271.7 mg, 0.806 mmol, 81% yield). ¹H NMR (400MHz, CHLOROFORM-d) δ 8.59 (d, *J*=5.3 Hz, 1H), 8.35 (s, 1H), 7.82 (s, 1H), 7.72 - 7.69 (m, 1H), 7.60 (dd, *J*=5.3, 1.3 Hz, 1H), 3.97 - 3.90 (m, 2H), 2.64 (s, 3H), 1.83 (dt, *J*=12.7, 6.1 Hz, 1H), 1.53 (t, *J*=5.5 Hz, 2H), 1.28 (s, 3H), 1.04 - 0.96 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 334.3 [(M+H)⁺, calcd C₁₈H₂₅ClN₃O, 334.2]; LC/MS retention time (method B): *t_R* = 1.49 min.

Example 239

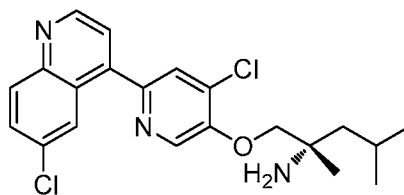
(S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (S)-1-((4,6-dichloropyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine bis(2,2,2-trifluoroacetate)

TFA (2 mL, 26.0 mmol) was added a solution of (S)-tert-butyl (1-((4,6-dichloropyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.146 g, 0.387 mmol) in DCM (4 mL) at room temperature. The reaction was stirred for 1.5 h at room temperature. The solvent was removed under reduced pressure and the crude

material was carried on without further purification. LCMS (ESI) m/e 259.9 [(M-NH₂)⁺, calcd C₁₂H₁₆Cl₂NO, 260.1]; LC/MS retention time (method B): t_R = 1.73 min.



5

Part B: (S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

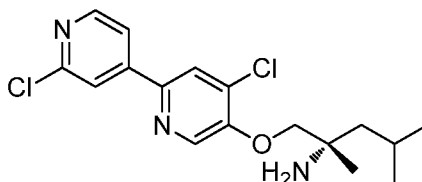
Suzuki coupling was performed as described in Example 77, Part D.

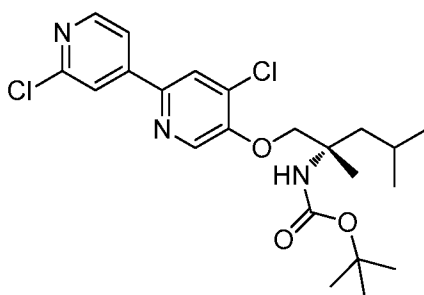
Obtained (S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (8.4 (S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (mg, 0.020 mmol, 22% yield over two steps).
¹H NMR (500MHz, DMSO-d₆) δ 9.01 (d, J =4.4 Hz, 1H), 8.71 (s, 1H), 8.35 (d, J =2.2 Hz, 1H), 8.14 (d, J =9.2 Hz, 1H), 8.04 (s, 1H), 7.83 (dd, J =8.8, 2.2 Hz, 1H), 7.74 (d, J =4.4 Hz, 1H), 4.06 (s, 2H), 1.89 - 1.80 (m, 1H), 1.52 - 1.40 (m, 2H), 1.18 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 403.8 [(M+H)⁺, calcd C₂₁H₂₄Cl₂N₃O, 404.1]; LC/MS retention time (method B): t_R = 1.91 min.

15

Example 240

20 (S)-1-((2',4'-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

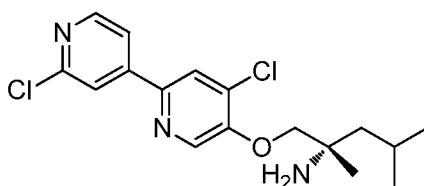




Part A: (S)-tert-butyl (1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

- 5 Obtained (S)-tert-butyl (1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (12.6 mg, 0.014 mmol, 7% yield). LCMS (ESI) m/e 476.1 $[(M+Na)^+]$, calcd $C_{22}H_{29}Cl_2N_3O_3Na$, 476.2; LC/MS retention time (method A): t_R = 2.52 min.



10

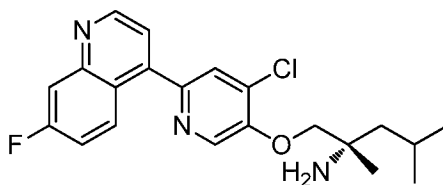
Part B: (S)-1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

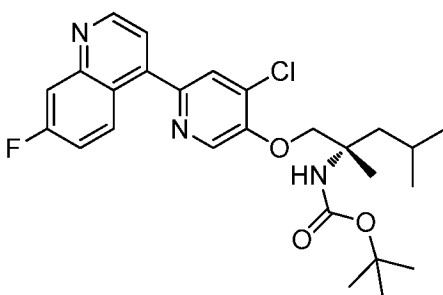
- TFA deprotection as described in Example 32. Obtained (S)-1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (4.9 mg, 0.014 mmol, 100% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.60 (s, 1H), 8.51 (d, $J=5.5$ Hz, 1H), 8.44 (s, 1H), 8.15 (s, 1H), 8.08 (dd, $J=5.1, 1.5$ Hz, 1H), 1.82 (dq, $J=12.8, 6.4$ Hz, 1H), 1.41 (t, $J=5.3$ Hz, 2H), 1.14 (s, 3H), 0.93 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 337.0 $[(M-NH_2)^+]$, calcd $C_{17}H_{19}Cl_2N_2O$, 337.1; LC/MS retention time (method B): t_R = 1.98 min.

20

Example 241

(S)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

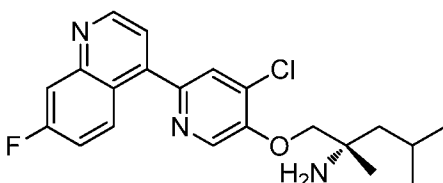




Part A: (S)-tert-butyl (1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

- 5 Obtained (*S*)-*tert*-butyl (1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (30.5 mg, 0.021 mmol, 20% yield). LCMS (ESI) *m/e* 488.2 [(M+H)⁺, calcd C₂₆H₃₂ClFN₃O₃, 488.2]; LC/MS retention time (method B): *t_R* = 2.37 min.



- 10 *Part B: (S)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine*

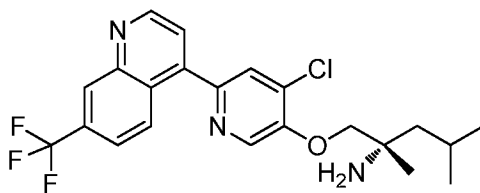
TFA deprotection as described in Example 32. Obtained (*S*)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (4.4 mg, 0.011 mmol, 18% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.01 (d, *J*=4.4 Hz, 1H), 8.68 (s, 1H), 8.33 (dd, *J*=9.4, 6.4 Hz, 1H), 8.01 (s, 1H), 7.85 (dd, *J*=10.5, 2.4 Hz, 1H), 7.66 (d, *J*=4.4 Hz, 1H), 7.60 - 7.53 (m, 1H), 4.04 (s, 2H), 1.85 (dt, *J*=12.7, 6.5 Hz, 1H), 1.45 (t, *J*=6.4 Hz, 2H), 1.18 (s, 3H), 0.96 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 388.1 [(M+H)⁺, calcd C₂₁H₂₄ClFN₃O, 388.2]; LC/MS retention time (method B): *t_R* = 1.82 min.

20

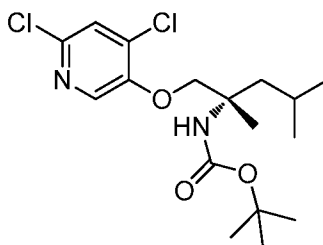
25

Example 242

(*S*)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



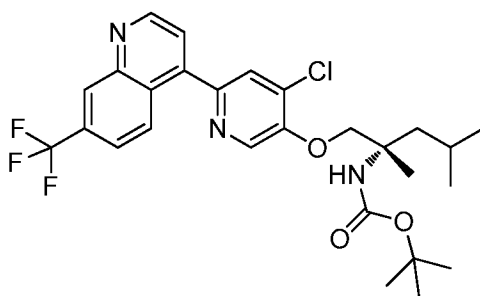
5



Part A: (*S*)-tert-butyl (1-((4,6-dichloropyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 53, Part A. Obtained (*S*)-tert-butyl (1-((4,6-dichloropyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (765.6 mg, 2.03 mmol, 74% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.05 - 8.02 (m, 1H), 7.35 (s, 1H), 4.55 (s, 1H), 4.30 (d, *J*=8.8 Hz, 1H), 4.11 (d, *J*=8.8 Hz, 1H), 1.91 - 1.75 (m, 2H), 1.58 - 1.48 (m, 1H), 1.41 - 1.38 (m, 12H), 0.98 (m, 6H). LCMS (ESI) *m/e* 399.0 [(M+Na)⁺, calcd C₁₇H₂₆Cl₂NaN₂O₃, 399.1]; LC/MS retention time (method B): *t_R* = 2.41 min.

15

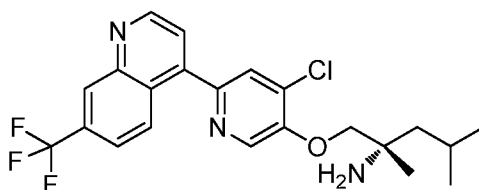


Part B: (*S*)-tert-butyl (1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

20

Suzuki coupling was performed as described in Example 77, Part D. Obtained (*S*)-tert-butyl (1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-

dimethylpentan-2-yl)carbamate (26.3 mg, 0.049 mmol, 33% yield). LCMS (ESI) m/e 538.1 $[(M+H)^+]$, calcd $C_{27}H_{32}ClF_3N_3O_3$, 538.2]; LC/MS retention time (method B): t_R = 2.51 min.

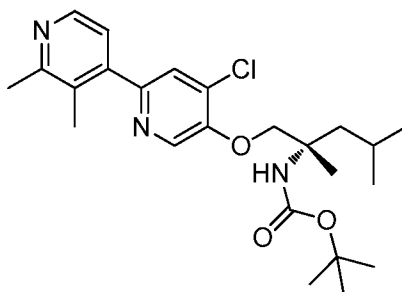
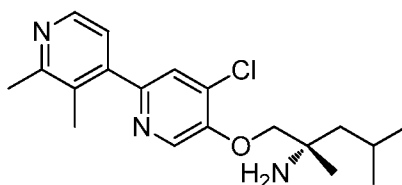


Part C: (S)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (S)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (17.7 mg, 0.040 mmol, 83% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.14 (d, $J=4.3$ Hz, 1H), 8.69 (s, 1H), 8.49 (d, $J=8.5$ Hz, 1H), 8.45 (s, 1H), 8.06 (s, 1H), 7.90 (d, $J=8.9$ Hz, 1H), 7.85 (d, $J=4.6$ Hz, 1H), 4.04 (s, 2H), 1.85 (dt, $J=12.5, 6.3$ Hz, 1H), 1.45 (t, $J=5.8$ Hz, 2H), 1.18 (s, 3H), 0.95 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 438.3 $[(M+H)^+]$, calcd $C_{22}H_{24}ClF_3N_3O$, 438.1]; LC/MS retention time (method A): t_R = 1.66 min.

Example 243

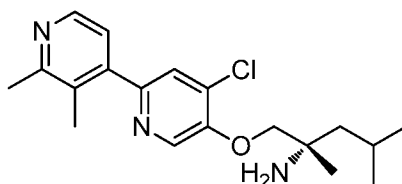
(S)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (*S*)-*tert*-butyl (1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 77, Part D.

Obtained (*S*)-*tert*-butyl (1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (23 mg, 0.014 mmol, 7% yield). LCMS (ESI) *m/e* 448.2 [(M+H)⁺, calcd C₂₄H₃₅ClN₃O₃, 448.2]; LC/MS retention time (method B): *t*_R = 2.14 min.



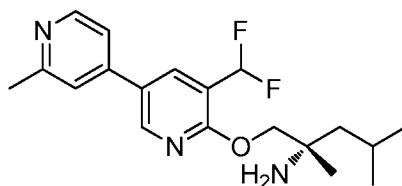
Part B: (*S*)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection as described in Example 32. Obtained (*S*)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (1.5 mg, 4.14 mol, 8% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.46 (d, *J*=5.1 Hz, 1H), 8.42 (s, 1H), 7.46 (s, 1H), 7.28 (br. s., 1H), 4.08 (br. s., 2H), 2.57 (s, 3H), 2.07 (s, 3H), 1.61 (br. s., 1H), 1.43 - 1.25 (m, 2H), 1.15 (br. s., 3H), 0.91 - 0.66 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 348.2 [(M+H)⁺, calcd C₁₉H₂₇ClN₃O, 348.2]; LC/MS retention time (method B): *t*_R = 1.34 min.

20

Example 244

(*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



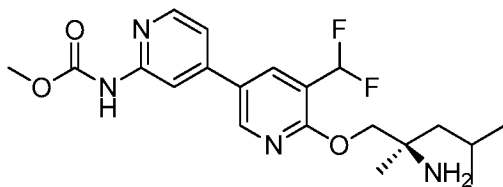
Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (9.8 mg, 0.028 mmol, 49% yield). ¹H NMR (500MHz, DMSO-d₆) δ 8.76 (s, 1H), 8.50 (d, *J*=5.2 Hz, 1H), 8.33 (s, 1H), 7.66 (s, 1H), 7.57 (d, *J*=4.9 Hz, 1H), 7.28

(t, $J=1.0$ Hz, 1H), 4.19 (s, 2H), 1.85 (s, 3H), 1.82 - 1.73 (m, 1H), 1.44 (qd, $J=13.9$, 5.5 Hz, 2H), 1.16 (s, 3H), 0.92 (d, $J=6.7$ Hz, 3H), 0.89 (d, $J=6.4$ Hz, 3H); LCMS (ESI) m/e 333.2 $[(M-NH_2)^+]$, calcd $C_{19}H_{23}N_2F_2O$, 333.2]; LC/MS retention time (method B): t_R = 1.46 min.

5

Example 245

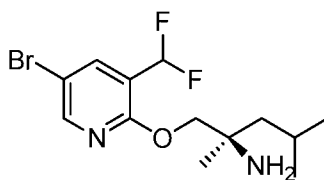
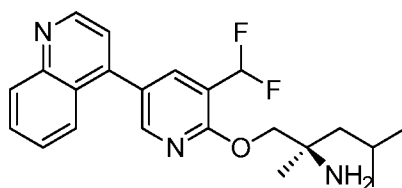
(*R*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate



10 Suzuki coupling was performed as described in Example 77, Part D. Obtained (*R*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate (13.3 mg, 0.032 mmol, 54% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.69 (s, 1H), 8.35 (d, $J=5.1$ Hz, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.44 (d, $J=3.7$ Hz, 1H), 7.39 - 7.14 (t, $J=44.0$ Hz, 1H), 4.15 (d, $J=2.6$ Hz, 2H), 3.71 (s, 3H),
15 1.84 - 1.73 (m, 1H), 1.40 (t, $J=6.1$ Hz, 2H), 1.13 (s, 3H), 0.92 (m, 6H); LCMS (ESI) m/e 392.2 $[(M-NH_2)^+]$, calcd $C_{20}H_{24}F_2N_3O_3$, 392.2]; LC/MS retention time (method B): t_R = 1.70 min.

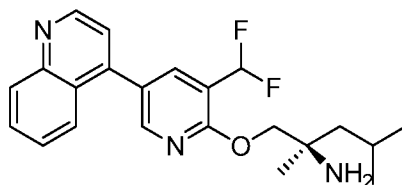
Example 246

20 (*R*)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Part A: (R)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as described in Example 193. Obtained (R)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (275 mg, 0.465 mmol, 55% yield). LCMS (ESI) m/e 320.1 $[(M-NH_2)^+]$, calcd $C_{13}H_{17}BrF_2NO$, 320.1]; LC/MS retention time (method B): t_R = 1.95 min.



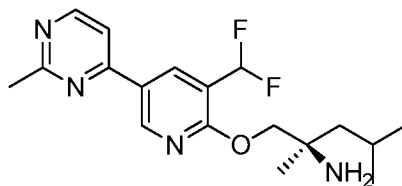
Part B: (R)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Suzuki coupling was performed as described in Example 77, Part D. Obtained (R)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (6.3 mg, 0.016 mmol, 24% yield). ^1H NMR (500MHz, DMSO- d_6) δ 8.98 (d, J =4.4 Hz, 1H), 8.52 (s, 1H), 8.16 - 8.12 (m, 2H), 7.87 - 7.80 (m, 2H), 7.69 - 7.62 (m, 1H), 7.56 (d, J =4.4 Hz, 1H), 7.29 (t, J =1.0 Hz, 1H), 4.19 (s, 2H), 1.87 - 1.78 (m, 1H), 1.49 - 1.38 (m, 2H), 1.16 (s, 3H), 0.94 (m, 6H), two exchangeable protons not observed; LCMS (ESI) m/e 386.2 $[(M+H)^+]$, calcd $C_{22}H_{26}F_2N_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.65 min.

20

Example 247

(R)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



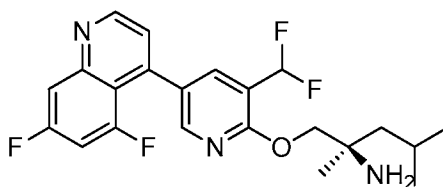
Suzuki coupling was performed as described in Example 77, Part D. Obtained (R)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (7.7 mg, 0.022 mmol, 37% yield). ^1H NMR (500MHz, DMSO- d_6) δ 9.12 (s, 1H), 8.77 (d, J =5.1 Hz, 1H), 8.68 (s, 1H), 7.98 (d, J =5.5 Hz,

1H), 7.42 - 7.16 (t, $J=55.0$ Hz, 1H), 4.18 (s, 2H), 2.69 (s, 3H), 1.85 - 1.75 (m, 1H), 1.41 (dd, $J=9.0, 5.7$ Hz, 2H), 1.14 (s, 3H), 0.92 (m, 6H); LCMS (ESI) m/e 334.1 [(M-NH₂)⁺, calcd C₁₈H₂₂F₂N₃O, 334.2]; LC/MS retention time (method B): t_R = 1.81 min.

5

Example 248

(*R*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

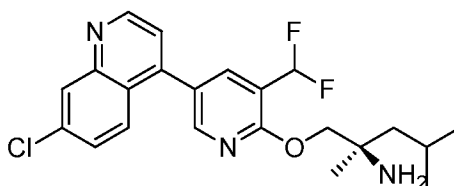


10 Suzuki coupling was performed as described in Example 77, Part D. Obtained (*R*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (8.4 mg, 0.020 mmol, 21% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.02 (d, $J=4.4$ Hz, 1H), 8.44 (s, 1H), 8.12 (br. s., 1H), 7.81 (d, $J=9.2$ Hz, 1H), 7.61 (ddd, $J=12.3, 9.5, 2.4$ Hz, 1H), 7.52 (d, $J=4.8$ Hz, 1H), 7.40 - 7.14 (t, $J=55.0$ Hz, 1H), 4.16 (s, 2H), 1.86 - 1.77 (m, 1H), 1.42 (dd, $J=7.9, 5.7$ Hz, 2H), 1.15 (s, 3H), 0.94 (m, 6H); LCMS (ESI) m/e 405.1 [(M-NH₂)⁺, calcd C₂₂H₂₁F₄N₂O, 405.2]; LC/MS retention time (method B): t_R = 2.01 min.

15

Example 249

(*R*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



20

Suzuki coupling was performed as described in Example 77, Part D. Obtained (*R*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (16.9 mg, 0.039 mmol, 34% yield). ¹H NMR (500MHz, DMSO-d₆) δ 9.01 (d, $J=4.4$ Hz, 1H), 8.52 (s, 1H), 8.19 (d, $J=2.2$ Hz, 1H), 8.16 (s, 1H), 7.87 (d, $J=9.2$ Hz, 1H), 7.69 (dd, $J=9.2, 2.2$ Hz, 1H), 7.60 (d, $J=4.4$ Hz, 1H),

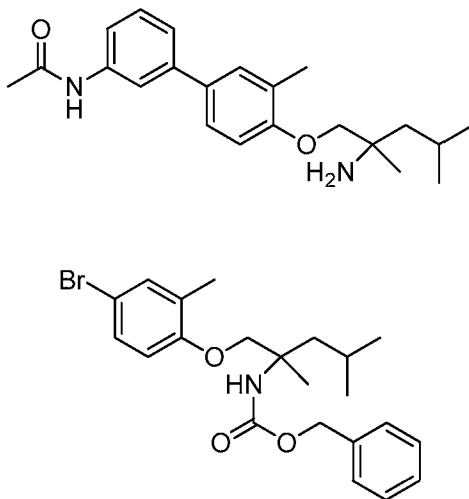
25

7.42 - 7.16 (t, $J=55.0\text{Hz}$, 1H), 4.19 (s, 2H), 1.85 - 1.77 (m, 1H), 1.49 - 1.37 (m, 2H), 1.16 (s, 3H), 0.94 (m, 6H); LCMS (ESI) m/e 403.1 $[(M-NH_2)^+]$, calcd $C_{22}H_{22}ClF_2N_2O$, 403.1]; LC/MS retention time (method B): $t_R = 1.97$ min.

5

Example 250

N-(4'-((2-amino-2,4-dimethylpentyl)oxy)-3'-methyl-[1,1'-biphenyl]-3-yl)acetamide

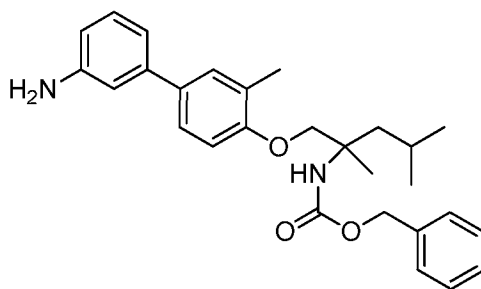


10

Part A: Benzyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 29, Part A. Obtained benzyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (33 mg, 0.076 mmol, 27% yield). LCMS (ESI) m/e 456.1 $[(M+Na)^+]$, calcd $C_{22}H_{28}BrNO_3Na$, 456.1]; LC/MS retention time (method B): $t_R = 2.55$ min.

15

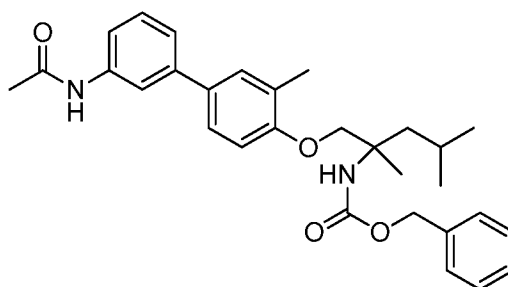


Part B: Benzyl (1-((3'-amino-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

20

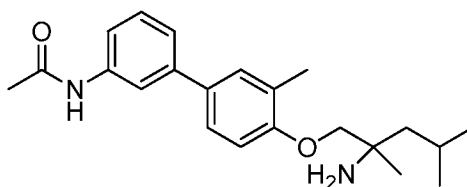
Suzuki reaction was performed as described in Example 193. Obtained benzyl (1-((3'-amino-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (21.1 mg, 0.047 mmol, 62% yield). ^1H NMR (400MHz,

CHLOROFORM-d) δ 7.38 - 7.29 (m, 7H), 7.21 (t, $J=7.8$ Hz, 1H), 6.99 - 6.94 (m, 1H), 6.88 (t, $J=1.9$ Hz, 2H), 6.65 (ddd, $J=7.9, 2.3, 0.9$ Hz, 1H), 5.06 (s, 2H), 4.93 (s, 1H), 4.13 (d, $J=8.8$ Hz, 1H), 3.99 (d, $J=8.8$ Hz, 1H), 3.73 (br. s., 2H), 2.28 (s, 3H), 1.92 - 1.77 (m, 2H), 1.72 - 1.65 (m, 1H), 1.48 (s, 3H), 0.98 (m, 6H); LCMS (ESI) m/e 447.5 $[(M+H)^+]$, calcd $C_{28}H_{35}N_2O_3$, 447.6]; LC/MS retention time (method A): t_R = 2.38 min.



Part C: Benzyl (1-((3'-acetamido-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Acetyl chloride (1 drop) was added to a solution of benzyl (1-((3'-amino-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.0221 g, 0.049 mmol) in CH_2Cl_2 (2 mL) at room temperature. The reaction was stirred for 10 min at room temperature before addition of triethylamine (1 drop). The reaction was stirred for 2 h the concentrated under reduced pressure. The residue was carried on without further purification. LCMS (ESI) m/e 489.5 $[(M+H)^+]$, calcd $C_{30}H_{37}N_2O_4$, 489.3]; LC/MS retention time (method A): t_R = 2.39 min.



Part D: N-(4'-((2-amino-2,4-dimethylpentyl)oxy)-3'-methyl-[1,1'-biphenyl]-3-yl)acetamide

A mixture of Pd/C (3 mg, 2.82 μ mol) and benzyl (1-((3'-acetamido-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (23.94 mg, 0.049 mmol) in ethanol (3 mL) was hydrogenated via a H_2 balloon at room temperature overnight. The reaction was filtered through a celite pad and washed with DCM.

The filtrate was concentrated and the residue was purified by reverse phase Prep HPLC. Obtained *N*-(4'-((2-amino-2,4-dimethylpentyl)oxy)-3'-methyl-[1,1'-biphenyl]-3-yl)acetamide (11.4 mg, 0.031 mmol, 64% yield) as an off-white solid. ¹H NMR (500MHz, DMSO-d₆) δ 9.99 (s, 1H), 7.82 (s, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.41 - 7.24 (m, 4H), 6.98 (d, *J*=8.5 Hz, 1H), 3.72 (d, *J*=3.1 Hz, 2H), 2.26 (s, 3H), 2.07 (s, 3H), 1.85 - 1.78 (m, 1H), 1.46 - 1.41 (m, 2H), 1.16 (s, 3H), 0.93 (t, *J*=6.3 Hz, 6H); LCMS (ESI) *m/e* 338.4 [(M-NH₂)⁺, calcd C₂₂H₂₈NO₂, 338.2]; LC/MS retention time (method A): *t*_R = 2.03 min.

10

BIOLOGICAL DATA

*Methods**AAK1 Kinase Assay*

The assays were performed in U-bottom 384-well plates. The final assay volume was 30 μl prepared from 15 μl additions of enzyme and substrates (fluoresceinated peptide (5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH₂ and ATP) and test compounds in assay buffer (10 mM Tris-HCL pH 7.4, 10 mM MgCl₂, 0.01% Tween-20 and 1.0 mM DTT). The reactions were initiated by the combination of bacterially expressed, GST-Xa-hAAK1 with substrates and test compounds. The reactions were incubated at room temperature for 3 hours and terminated by adding 60 μl of 35 mM EDTA buffer to each sample. The reactions were analyzed on the Caliper LabChip 3000 (Caliper, Hopkinton, MA) by electrophoretic separation of the fluorescent substrate and phosphorylated product. Inhibition data were calculated by comparison to EDTA quenched control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assays are ATP, 22 μM; (5-FAM)-Aha-KEEQSQITSQVTGQIGWR-NH₂, 1.5 μM; GST-Xa-hAAK1, 3.5 nM; and DMSO, 1.6%. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC₅₀). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC₅₀ values were derived by non-linear regression analysis. Results are shown in Table 1.

Table 1

Example	AAK1 IC ₅₀ (nM)
1	2.7
2	3.0
3	0.30
4	2.8
5	0.50
6	0.47
7	0.42
8	0.53
9	-
10	10
11	3.3
12	1.6
13	1.1
14	0.87
15	0.81
16	6.6
17	24
18	5.0
19	0.36
20	0.34
21	0.74
22	0.65
23	0.76
24	0.63
25	1.0
26	0.69
27	1.0
28	1.2

29	0.67
30	1.4
31	4.5
32	4.5
33	0.32
34	15
35	0.77
36	0.89
37	0.51
38	0.79
39	3.2
40	8.7
41	3.8
42	3.3
43	0.64
44	2.8
45	1.2
46	0.86
47	0.77
48	4.6
49	2.6
50	0.38
63	24
64	1.1
65	42
66	0.65
67	4.7
68	2.6
69	0.76
70	2.3
71	0.55
72	0.53

73	0.51
74	0.07
75	34
76	1.7
77	0.92
78	0.49
79	16
80	19
81	7.8
82	0.85
83	1.8
84	2.2
85	0.32
86	1.2
87	0.87
88	0.46
89	0.66
90	2.6
91	12.1
92	5.4
93	33
94	4.7
95	39
96	3.0
97	142
98	10
99	31
100	6.8
101	27
102	1.3
103	0.68
104	0.83

105	0.72
106	0.62
107	50
108	106
109	340
110	3.5
111	650
112	970
113	43
114	1400
115	13
116	0.93
117	1.0
118	0.85
119	3.2
120	0.51
121	0.30
122	0.51
123	2.2
124	1.2
125	1.6
126	0.80
127	6.2
128	3.5
129	1.4
130	1.4
131	0.82
132	1.5
133	0.92
134	4.4
135	3.5
136	4.8

137	27
138	35
139	0.77
140	470
141	1.8
142	4.1
143	0.45
144	1.3
145	0.24
146	0.19
147	0.56
148	0.34
149	1.5
150	24
151	
152	0.68
153	1.9
154	6.8
155	57
156	110
157	19
158	5.4
159	1.5
160	0.8
161	1.7
162	530
163	1100
164	254
165	21
166	20
167	1040
168	58

169	101
170	285
171	48
172	1295
173	42
174	54
175	17
176	53
177	8.7
178	150
179	2.0
180	24
181	1.9
182	8.7
183	8.8
184	3.3
185	66
186	18
187	2.2
188	92
189	0.49
190	1.2
191	0.99
192	9.6
193	2.9
194	1.5
195	0.25
196	0.20
197	0.31
198	2.2
199	1.0
200	1.2

201	0.64
202	3.1
203	21
204	0.23
205	0.70
206	4.3
207	19
208	4.6
209	21
210	79
211	491
212	1024
213	22
214	0.86
215	197
216	25
217	0.56
218	1.0
219	0.59
220	0.38
221	4.1
222	1.2
223	0.88
224	1.1
225	0.74
226	0.93
227	0.93
228	22
229	1.0
230	1.1
231	0.47
232	0.41

233	0.73
234	3.2
235	0.36
236	0.98
237	1.4
238	2.1
239	0.39
240	2.2
241	0.86
242	1.9
243	1071
244	262
245	11
246	26
247	234
248	74
249	27
250	659
251	1098

AAK1 Knockout Mice

Mice homozygous (-/-) for the disruption of the AAK1 gene were prepared by two methods; gene trapping and homologous recombination.

- 5 Gene trapping is a method of random insertional mutagenesis that uses a fragment of DNA coding for a reporter or selectable marker gene as a mutagen. Gene trap vectors have been designed to integrate into introns or genes in a manner that allows the cellular splicing machinery to splice vector encoded exons to cellular mRNAs. Commonly, gene trap vectors contain selectable marker sequences that are
- 10 preceded by strong splice acceptor sequences and are not preceded by a promoter. Thus, when such vectors integrate into a gene, the cellular splicing machinery splices exons from the trapped gene onto the 5' end of the selectable marker sequence. Typically, such selectable marker genes can only be expressed if the vector encoding

the gene has integrated into an intron. The resulting gene trap events are subsequently identified by selecting for cells that can survive selective culture.

Embryonic stem cells (Lex-1 cells from derived murine strain A129), were mutated by a process involving the insertion of at least a portion of a genetically engineered vector sequence into the gene of interest, the mutated embryonic stem
5 cells were microinjected into blastocysts which were subsequently introduced into pseudopregnant female hosts and carried to term using established methods. *See, e.g., "Mouse Mutagenesis", 1998, Zambrowicz et al., eds., Lexicon Press, The Woodlands, TX.* The resulting chimeric animals were subsequently bred to produce
10 offspring capable of germline transmission of an allele containing the engineered mutation in the gene of interest.

AAK1-gene disrupted mice were also made by homologous recombination. In this case, the second coding exon of the murine AAK1 gene (see GenBank Accession Number NM_177762) was removed by methods known in the art. *See, e.g., U.S. Patent Nos. 5,487,992, 5,627,059, and 5,789,215.*
15

Mice homozygous (-/-) for the disruption of the AAK1 gene were studied in conjunction with mice heterozygous (+/-) for the disruption of the AAK1 gene, and wild-type (+/+) litter mates. During this analysis, the mice were subject to a medical work-up using an integrated suite of medical diagnostic procedures designed to
20 assess the function of the major organ systems in a mammalian subject.

Homozygous (-/-) "knockout" mice were studied in conjunction with their heterozygous (+/-) and wild-type (+/+) litter mates. Disruption of the AAK1 gene was confirmed by Southern analysis. Expression of the murine homolog of AAK1 was detected by RT-PCR in murine brain; spinal cord; eye; thymus; spleen; lung;
25 kidney; liver; skeletal muscle; bone; stomach, small intestine and colon; heart; adipose; asthmatic lung; LPS liver; blood; banded heart; aortic tree; prostate; and mammary gland (5 week virgin, mature virgin, 12 DPC, 3 day post-partum (lactating), 3 day post-weaning (early involution), and 7 day post-weaning (late involution)).

30 AAK1 homozygous (-/-) and their wild-type (+/+) littermates were tested using the formalin paw test in order to assess their acute and tonic nociceptive responses. For these tests, Automatic Nociception Analyzers (purchased from the Ozaki lab at University of California, San Diego) were used. A metal band was

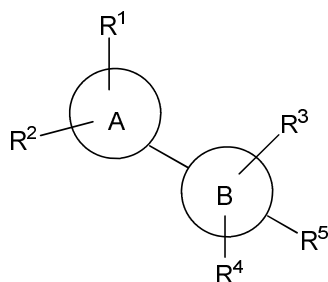
placed around the left hind paw of each mouse 30 minutes prior to testing. After the 30-minute acclimation period, 20 μ l of 5% formalin is subcutaneously injected in the dorsal surface of the left hind paw. Mice were individually housed in cylindrical chambers for 45 minutes. Fresh 5 % formalin solution was prepared by diluting formaldehyde (Formalde-fresh 20%, Fisher Scientific, Fair Lawn, NJ) with distilled water. Investigatory compounds were administered 30 minutes prior to formalin injection.

A computer recorded flinches per minute, total flinches for phase I (acute phase = first 8 minutes), and total flinches for phase II (tonic phase = time between minutes 20 - 40) through an electromagnetic field. See Yaksh TL, Ozaki G, McCumber D, Rathbun M, Svensson C, Malkmus S, Yaksh MC. *An automated flinch detecting system for use in the formalin nociceptive bioassay. J Appl Physiol.*, 2001; 90:2386-402. As shown in Figure 1, phase 1 and phase 2 data were obtained using homozygous (-/-) mice females (n = 16), wild-type females (n = 15), homozygous (-/-) mice males (n = 9), and wild-type males (n = 18). In all groups and in both phases, the AAK1 homozygous (-/-) mice exhibited significantly less recorded paw flinching than their wild-type (+/+) littermates.

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

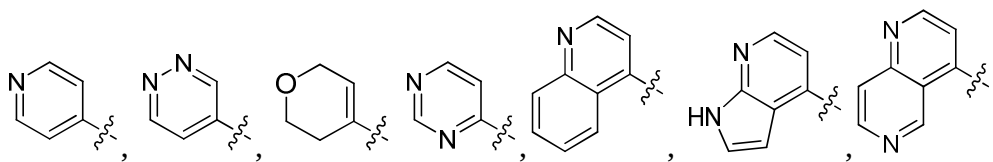
1. A compound of formula (I)

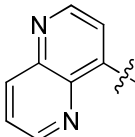


(I),

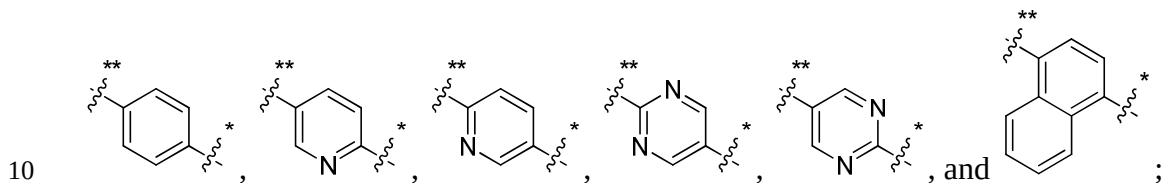
5 or a pharmaceutically acceptable salt thereof, wherein:

A is selected from



and ; wherein “~” denotes the point of attachment to B;

B is selected from



wherein “*” indicates the point of attachment to R5 and “**” indicates the point of attachment to ring A;

R^1 is selected from hydrogen, amino, $-CO_2H$, difluoromethyl, ethyl, halo, hydroxymethyl, methoxy, methyl, $-NHC(O)CH_3$, $-NHCO_2CH_3$, trifluoromethoxy, and trifluoromethyl;

15

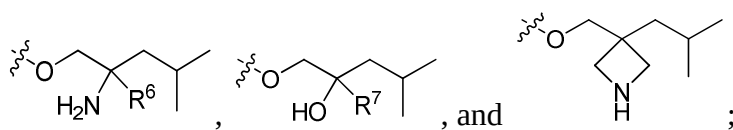
R^2 is selected from hydrogen, cyano, $-CH_2OH$, halo, and methyl;

R^3 is selected from hydrogen, cyano, cyclopropyl, difluoromethyl, halo, hydroxymethyl, methoxy, methyl, methylsulfonyl, trifluoromethoxy, trifluoromethyl, $-CH_2N(CH_3)_2$, and a five-membered aromatic ring containing one, two, or three

20

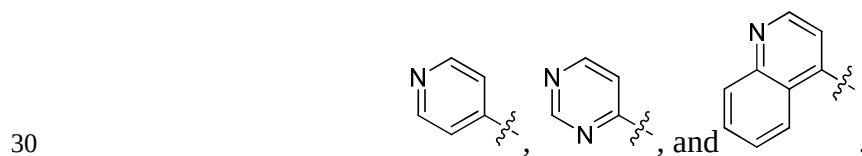
R^4 is selected from hydrogen, halo, and methyl;

R⁵ is selected from

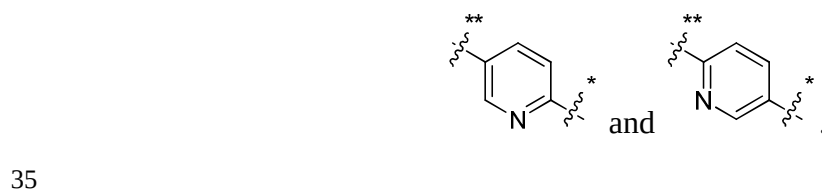


R⁶ is selected from hydrogen, ethyl, fluoromethyl, difluoromethyl, methyl,
 25 and trifluoromethyl; and
 R⁷ is methyl.

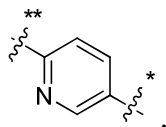
2. A compound of claim 1, or a pharmaceutically acceptable salt thereof,
 wherein A is selected from



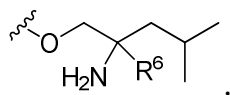
3. A compound of claim 1, or a pharmaceutically acceptable salt thereof,
 wherein B is selected from



4. A compound of claim 3, or a pharmaceutically acceptable salt thereof,
 wherein B is



40 5. A compound of claim 1 wherein R⁵ is



6. A compound according to claim 1 selected from
 (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-
 45 yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide;

50 (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-aminopyridin-4-yl)benzonitrile;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide;

55 (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide;

60 (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide;

(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluoro-5-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide;

65 (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide;

(*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate;

(*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate;

70 (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile;

(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methoxypyridin-4-yl)benzonitrile;

(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile;

75 (*S*)-1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-amine;

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide;

(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 80 (trifluoromethyl)phenyl)pyridin-2-yl)carbamate;
 (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-
 yl)acetamide;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-
 2-yl)carbamate;
 85 (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 (difluoromethyl)phenyl)pyridin-2-yl)acetamide;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 (difluoromethyl)phenyl)pyridin-2-yl)carbamate;
 (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 90 (trifluoromethoxy)phenyl)pyridin-2-yl)acetamide;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 (trifluoromethoxy)phenyl)pyridin-2-yl)carbamate;
 (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-
 yl)acetamide;
 95 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-
 2-yl)carbamate;
 methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-
 yl)carbamate;
 methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-
 100 yl)carbamate;
 methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-
 2-yl)carbamate;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 (hydroxymethyl)phenyl)pyridin-2-yl)carbamate;
 105 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 cyclopropylphenyl)pyridin-2-yl)carbamate;
 (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-5-
 (hydroxymethyl)pyridin-2-yl)acetamide;
 (S)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-
 110 dimethylpentan-2-amine;

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyridin-4-yl)benzonitrile;

(S)-1-(2-(difluoromethyl)-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

115 (S)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(4-(3-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(4-(5-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-

120 dimethylpentan-2-amine;

(S)-1-(4-(2-fluoro-3-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(4-(2,3-difluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

125 (S)-2,4-dimethyl-1-(4-(pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

(S)-1-(4-(2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-

130 (trifluoromethyl)phenoxy)pentan-2-amine;

(S)-1-(4-(3-methoxypyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(4-(3-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

135 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile;

(S)-1-(2-cyclopropyl-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(2-(difluoromethyl)-4-(2-methylpyridin-4-yl)phenoxy)-2,4-

140 dimethylpentan-2-amine;

methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate;

(S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methyl-[3,4'-bipyridin]-2'-yl)carbamate;

145 (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate;

(S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate;

(S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate;

150 (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methoxy-[3,4'-bipyridin]-2'-yl)carbamate;

(S)-1-((2'-chloro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

155 (S)-1-((2'-(difluoromethyl)-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-(difluoromethyl)-[3,4'-bipyridine]-5-carbonitrile;

(S)-1-((5-chloro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

160 (S)-1-((2',5-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((5-methoxy-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate;

165 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate;

(S)-1-((2',6-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate;

170 (S)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate;

175 (S)-2,4-dimethyl-1-(4-(quinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;
 (S)-2,4-dimethyl-1-(2-(trifluoromethyl)-4-(7-(trifluoromethyl)quinolin-4-yl)phenoxy)pentan-2-amine;
 (S)-1-(4-(7-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-
 180 dimethylpentan-2-amine;
 (S)-1-(4-(5,7-difluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;
 (S)-1-(4-(6-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;
 185 (S)-1-(2-cyclopropyl-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;
 1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((5-(7-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5,7-difluoroquinolin-4-
 190 yl)nicotinonitrile;
 (S)-1-((3-chloro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((3-methoxy-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 195 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)nicotinonitrile;
 (S)-2,4-dimethyl-1-((2-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine;
 (S)-2,4-dimethyl-1-((4-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-
 200 amine;
 (S)-1-((2-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;
 205 (S)-1-(4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile;

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,5-naphthyridin-4-yl)benzonitrile;

210 (S)-1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)quinoline-7-carbonitrile;

215 (S)-2,4-dimethyl-1-(2-methyl-4-(2-methylpyridin-4-yl)phenoxy)pentan-2-amine;

(S)-1-(2-fluoro-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-(4-(2-fluoropyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine;

220 (S)-1-(2-fluoro-4-(2-fluoropyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-fluoropyridin-4-yl)benzonitrile;

225 (S)-1-((2'-fluoro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)quinoline-7-carbonitrile;

(S)-1-((5-fluoro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;

230 (S)-1-((3-fluoro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)quinoline-7-carbonitrile;

235 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate;

(S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile;

(S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(7-methylquinolin-4-
 240 yl)benzonitrile;
 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(3-fluoro-2-methylpyridin-4-
 yl)benzonitrile;
 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(quinolin-4-yl)benzonitrile;
 (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5-fluoro-2-methylpyridin-4-
 245 yl)benzonitrile;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-5-
 fluoropyridin-2-yl)carbamate;
 (S)-1-((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-
 2-amine;
 250 methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-
 yl)carbamate;
 (S)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile;
 (S)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine;
 (S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-
 255 methylnicotinic acid;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 ((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate;
 (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-
 (methylsulfonyl)phenyl)pyridin-2-yl)carbamate;
 260 (S)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-
 (methylsulfonyl)phenoxy)pentan-2-amine;
 (S)-2,4-dimethyl-1-(2-(methylsulfonyl)-4-(quinolin-4-yl)phenoxy)pentan-2-
 amine;
 (S)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-
 265 dimethylpentan-2-amine;
 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-
 bipyridin]-2'-yl)carbamate;
 (S)-1-((2-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 270 (S)-1-((6-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;

(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

(S)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

((S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-6-(6-(trifluoromethoxy)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-
 305 dimethylpentan-2-amine;
 (S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((6-(6-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 310 (S)-1-((2-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((2-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 315 dimethylpentan-2-amine;
 (S)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 320 (S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-
 yl)oxy)pentan-2-amine;
 (S)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-
 yl)oxy)pentan-2-amine;
 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-
 325 bipyridin]-2'-yl)carbamate;
 (S)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 330 (S)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-((4-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-
 dimethylpentan-2-amine;
 (S)-1-(2-(difluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-
 335 dimethylpentan-2-amine;

(*S*)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine ;

(*S*)-1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

340 (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate;

(*S*)-1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate;

345 (*S*)-1-((2'-chloro-6-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-((2'-chloro-6-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

350 (*S*)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

((*S*)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-((4-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

355 (*S*)-1-((2-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(*R*)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine;

360 (*R*)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine;

(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

(*R*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

365 (*R*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*R*)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

370 (*R*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*R*)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*R*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-

375 dimethylpentan-2-amine;

(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate;

(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

380 (*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-methyl (4-(difluoromethyl)-5-((2-hydroxy-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate;

(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-

385 dimethylpentan-2-ol;

(*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

390 (*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate;

(*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-

395 methylpentan-2-amine;

(*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine;

(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine;

400 (R)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-
4-methylpentan-2-amine;

(S)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-
(fluoromethyl)-4-methylpentan-2-amine;

(R)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-
405 (fluoromethyl)-4-methylpentan-2-amine;

(S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-
yl)acetamide;

(S)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

410 (S)-1-((3-chloro-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-
415 dimethylpentan-2-amine;

(S)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

420 (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-
bipyridin]-2'-yl)carbamate;

(S)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-
425 dimethylpentan-2-amine;

(S)-1-((2',5-bis(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

430 (S)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-
dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(7-(trifluoromethyl)quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((5-(difluoromethyl)-2',3'-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-

435 dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-1-((3-(difluoromethyl)-5-(7-methylquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

440 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate;

(S)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;

(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-

445 2-yl)carbamate;

(S)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine;

(S)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate;

(S)-methyl (4-(2-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-5-yl)pyridin-2-

450 yl)carbamate;

(S)-2,4-dimethyl-1-((2',4,6-trimethyl-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine;

(S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4,6-dimethyl-[2,4'-bipyridin]-2'-yl)carbamate;

455 (S)-2,4-dimethyl-1-(4-(quinazolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

(S)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-2,4-dimethyl-1-(4-(2-methylquinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

460 (S)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

465 (S)-2,4-dimethyl-1-((5-(quinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)pentan-2-amine;
 (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate;
 (S)-2,4-dimethyl-1-((2'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)pentan-2-amine;
 470 (S)-1-((5-(6-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((5-(6-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 475 (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((5-(7-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((6-(5,7-difluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 480 (S)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((2',4'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 485 (S)-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 490 (S)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 495 (S)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

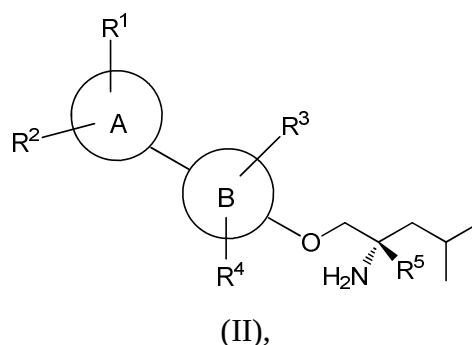
(S)-1-((4-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-chloro-[2,4'-bipyridin]-2'-yl)carbamate;
 500 (S)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 505 (S)-1-((2',4'-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;
 510 (S)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine;
 (R)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate;
 515 (R)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 (R)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 520 (R)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine; and
 (R)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;
 525 or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 selected from

(S)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

530 (S)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;
 (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate;
 (S)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-
 535 dimethylpentan-2-amine;
 (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine;
 540 (S)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 (S)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-
 545 dimethylpentan-2-amine; and
 (S)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine;
 or a pharmaceutically acceptable salt thereof.

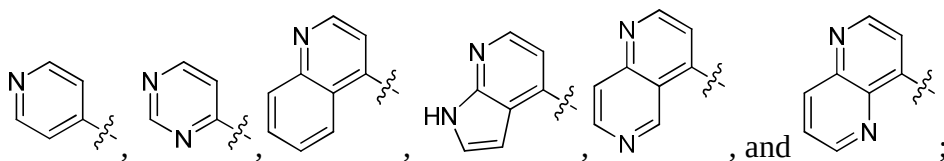
550 8. A compound of formula (II)



or a pharmaceutically acceptable salt thereof, wherein:

A is selected from

555



wherein “” denotes the point of attachment to B;

B is selected from phenyl and pyridinyl;

R¹ is selected from hydrogen, difluoromethyl, halo, methoxy, methyl, –
NHC(O)CH₃,

560 -NHCO₂CH₃, and trifluoromethyl;

R² is selected from hydrogen, -CH₂OH, and halo;

R³ is selected from hydrogen, cyano, cyclopropyl, difluoromethyl, halo,
hydroxymethyl, methoxy, methyl, trifluoromethoxy, trifluoromethyl, and a five-
membered aromatic ring containing one, two, or three heteroatoms selected from

565 nitrogen, oxygen, and sulfur;

R⁴ is selected from hydrogen, halo, and methyl; and

R⁵ is selected from hydrogen, ethyl, fluoromethyl, difluoromethyl, methyl,
and trifluoromethyl.

570 9. A compound according to claim 7 which is (S)-1-((2',6-bis(difluoromethyl)-
[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine; or a pharmaceutically
acceptable salt thereof.

10. A composition comprising a pharmaceutically acceptable amount of a
575 compound of anyone of claims 1 to 9, or a pharmaceutically acceptable salt thereof,
and a pharmaceutically acceptable carrier.

11. A compound of anyone of claims 1 to 9, or a pharmaceutically acceptable salt
thereof for use in the treatment or management of a disease or a disorder mediated by
580 AAK1activity.

12. The compound or pharmaceutically acceptable salt thereof for use according
to claim 11, wherein the disease or disorder is selected from Alzheimer's disease,
bipolar disorder, pain, Parkinson's disease, and schizophrenia.

585

13. The compound or pharmaceutically acceptable salt thereof for use according to claim 12 wherein the pain is neuropathic pain.

14. The compound or pharmaceutically acceptable salt thereof for use according to claim 13 wherein the neuropathic pain is fibromyalgia or peripheral neuropathy.

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