(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 April 2017 (06.04.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/059085 A1

(51) International Patent Classification:
C07D 401/04 (2006.01) *C07D 239/26* (2006.01)
C07D 213/75 (2006.01) *C07D 239/30* (2006.01)
C07D 239/42 (2006.01) *C07D 239/34* (2006.01)
C07D 401/14 (2006.01) *C07D 471/04* (2006.01)
C07D 413/14 (2006.01) *C07D 213/26* (2006.01)
C07D 213/73 (2006.01) *C07D 213/61* (2006.01)
C07D 213/85 (2006.01) *C07D 213/63* (2006.01)
C07D 237/20 (2006.01)

(21) International Application Number:
PCT/US2016/054471

(22) International Filing Date:
29 September 2016 (29.09.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3170/DEL/15 1 October 2015 (01.10.2015) IN

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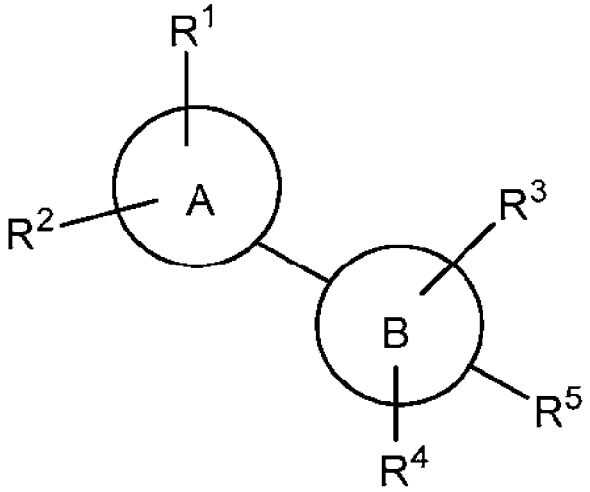
[Continued on next page]

(54) Title: BIARYL KINASE INHIBITORS

(57) Abstract: The present disclosure is directed to biaryl compounds of formula (I) which can inhibit AAKl (adaptor associated kinase 1), compositions comprising such compounds and their use for treating e.g. pain, Alzheimer's disease, Parkinson's disease and schizophrenia.



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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

BIARYL KINASE INHIBITORS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority of Indian Provisional Application Serial 3170/DEL/15 filed October 1, 2015 which is herein incorporated by reference in its entirety.

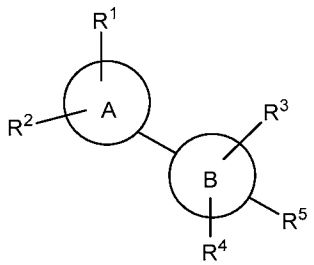
The present disclosure is generally directed to compounds which can inhibit adaptor associated kinase 1 (AAK1), compositions comprising such compounds, and methods for inhibiting AAK1.

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 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 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).

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 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.

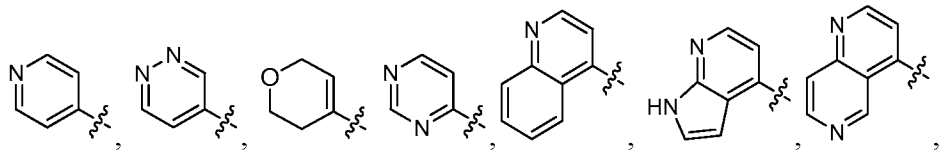
In its first aspect the present disclosure provides a compound of formula (I)
A compound of formula (I)

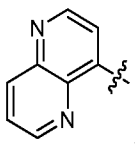


(I),

or a pharmaceutically acceptable salt thereof, wherein:

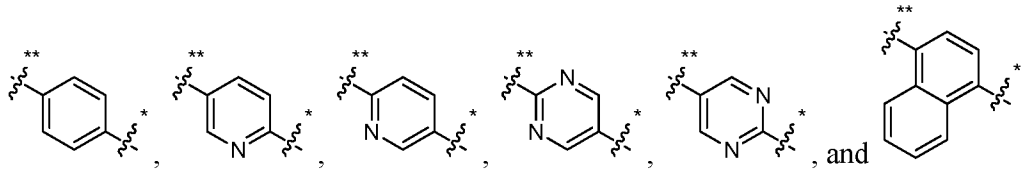
A is selected from



and 

; wherein "$\sim$" 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;

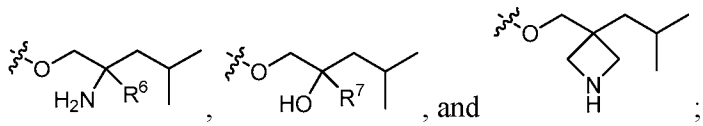
R^1 is selected from hydrogen, amino, $-CO_2H$, difluoromethyl, ethyl, halo, hydroxymethyl, methoxy, methyl, $-NHC(O)CH_3$, $-NHCO_2CH_3$, trifluoromethoxy, and trifluoromethyl;

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 heteroatoms selected from nitrogen, oxygen, and sulfur;

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

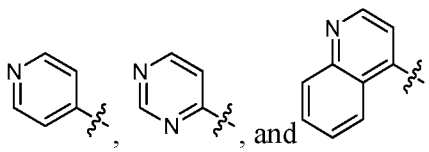
R^5 is selected from



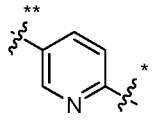
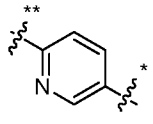
R^6 is selected from hydrogen, ethyl, fluoromethyl, difluoromethyl, methyl, and trifluoromethyl; and

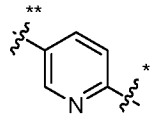
R^7 is methyl.

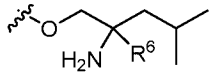
In a first embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein A is selected from



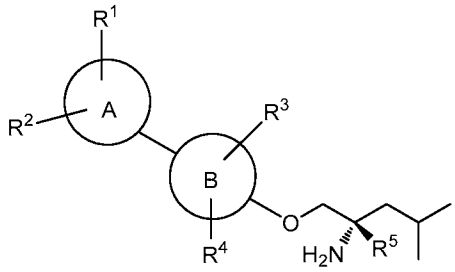
In a second embodiment of the first aspect the present disclosure provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein B is selected from

 and  .

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 R^5 is  .

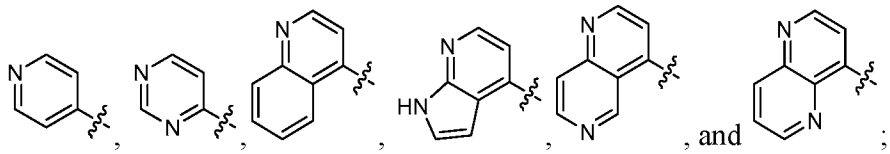
In a second aspect the present disclosure provides a compound of formula (II)



(II),

or a pharmaceutically acceptable salt thereof, wherein:

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, –$NHC(O)CH_3$,

-$NHCO_2CH_3$, and trifluoromethyl;

R^2 is selected from hydrogen, -CH_2OH, and halo;

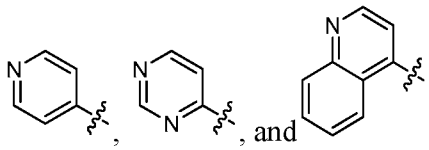
R^3 is selected from hydrogen, cyano, cyclopropyl, difluoromethyl, halo, hydroxymethyl, methoxy, methyl, trifluoromethoxy, trifluoromethyl, and a five-

membered aromatic ring containing one, two, or three heteroatoms selected from nitrogen, oxygen, and sulfur;

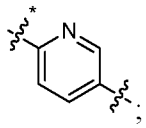
R^4 is selected from hydrogen, halo, and methyl; and

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



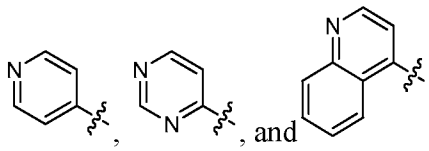
In a second embodiment of the second aspect the present disclosure provides a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein B is pyridinyl. In a third embodiment B is .



wherein "*" denotes the point of attachment to A and "~" denotes the point of attachment to the oxygen atom.

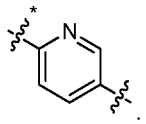
In a fourth embodiment of the second aspect the present disclosure provides a compound of formula (II), or a pharmaceutically acceptable salt thereof, wherein wherein

A is selected from



and

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 AAK1activity, 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.

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:

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.

In some instances, the number of carbon atoms in any particular group is denoted before the recitation of the group. For Example, the term "C_{1-6} 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.

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 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.

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

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 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 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, 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 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, diydrochloride, dihydroiodide, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylproprionate, 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

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 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, 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 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 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 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 (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, fludrocortisones, 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), 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 (*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 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 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-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, 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 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 (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 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.

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 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.

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. 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 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 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 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 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 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, 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 phopholipids, such as cholesterol, stearylamine, or phophatidylcholines.

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 polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palitoyl 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, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, 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 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 carrier is a solid include a course 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 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 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 soutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions 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 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; Ph_3P 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

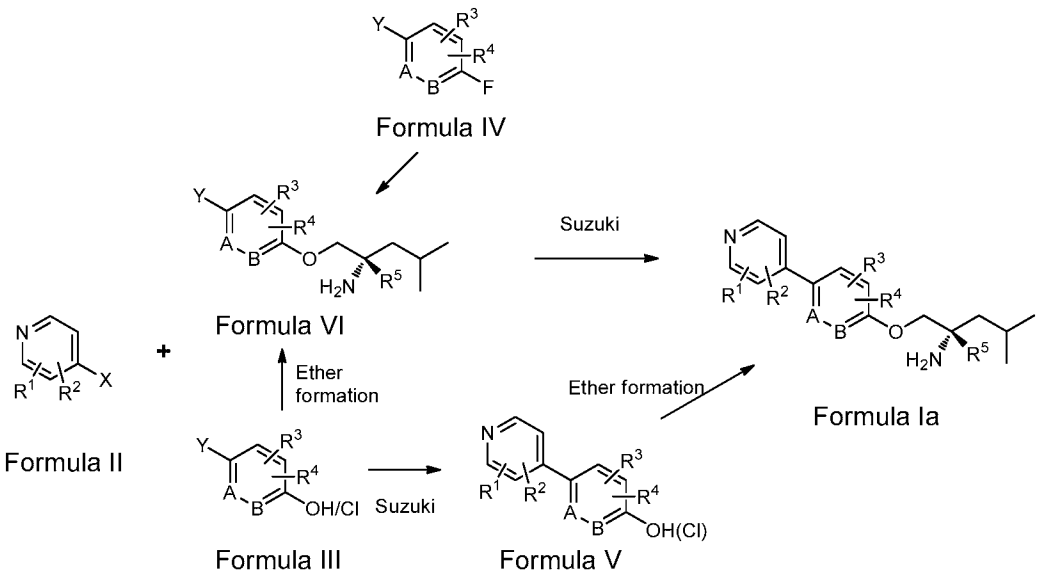
diphenylphosphinoferrocene; TFA for trifluoracetic acid; NMP for *N*-methylpyrrolidine; CBz or Cbz for benzyloxycarbonyl; DCM for dichloromethane; IPA for isopropyl alcohol; DMAP for *N*,*N*-dimethylaminopyridine; BOC or Boc for *tert*-butoxycarbonyl; $(BOC)_2O$ for di-tert-butyl dicarbonate/ DMF for *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 trifloride; BuOH for n-butanol; n-BuLi for n-butyllithium; NBS for N-bromosuccinimide; LAH for lithium aluminum hydride; DMF for N,N-dimethylformamide; dppf for 1,1'-bis(diphenylphosphino)ferrocene; TosMIC or TOSMIC for tosylmethyl isocyanide; TEA for triethylamine; PMB for p-methoxybenzyl; Ac for acetyl; DDQ for 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; and AIBN for 2,2'-azoisobutyronitrile.

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.

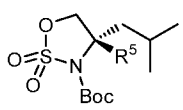
Compounds of Formula Ia can be synthesized following General Scheme I. The two key reactions, Suzuki coupling and ether formation, could alternate as shown depending on the commercially available starting materials. The Suzuki coupling substrates, boronic acids/boronates, were either commercially available or prepared from corresponding halogen intermediates (Cl/Br/I) with various standard literature conditions. The ether formation can be achieved by SN_{AR} 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.

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, 3µm; 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:

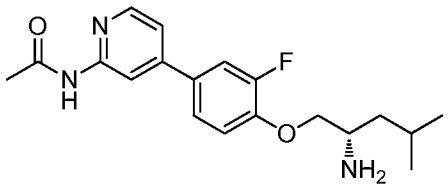
Column : Phenomenex LUNA C18, 30x2, 3µm; Solvent A = 10 % MeOH: 90% Water:0.1%TFA; Solvent B = 90% MeOH:10% Water:0.1%TFA; Flow rate: 1 ml/min; Starting B = 0%; Final B = 100%; Gradient time = 2 min; Run time: 3 min.

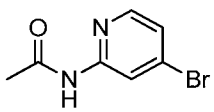
LC/MS Method C:

Column : Phenomenex LUNA C18, 30x2, 3µm; 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.

Example 1

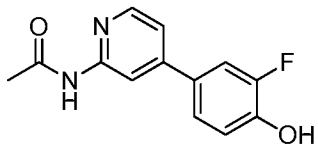
(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide





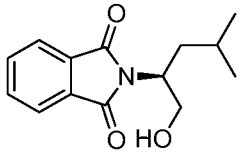
Part A: N-(4-bromopyridin-2-yl)acetamide

To a mixture of 4-bromopyridin-2-amine (3.11 g, 17.98 mmol) in CH_2Cl_2 (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 was quenched with water and diluted with EtOAc. The layers were separated. The organic layer was washed with water, brine, dried (Na_2SO_4) 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.



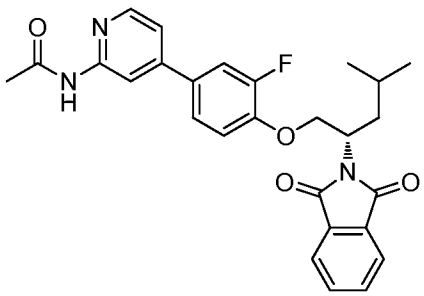
Part B: N-(4-(3-fluoro-4-hydroxyphenyl)pyridin-2-yl)acetamide

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 (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 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.



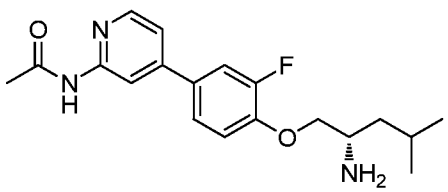
Part C: (S)-2-(1-hydroxy-4-methylpentan-2-yl)isoindoline-1,3-dione

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) 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-dioxoisoindolin-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), Ph_3P (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 $C_{27}H_{27}F_1N_3O_4$, 476.2]; LC/MS retention time (method A): t_R = 2.21 min.



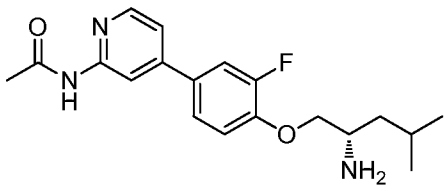
Part E: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

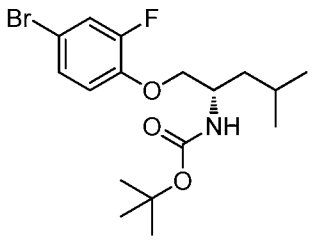
To a 50 mL round-bottomed flask was added (*S*)-*N*-(4-(4-((2-(1,3-dioxoisoindolin-2-yl)-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

(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): ^{1}H 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.

Alternative Synthesis of Example 1

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

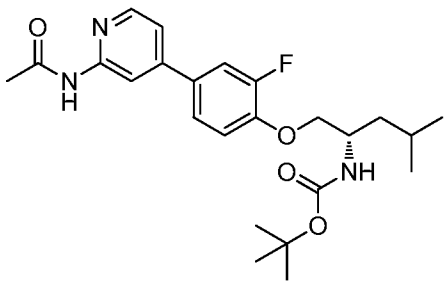




Part 2A: (S)-tert-butyl (1-(4-bromo-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate

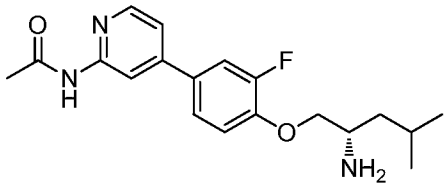
To a 15 mL vial was added (*S*)-*tert*-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (172 mg, 0.792 mmol), Ph_3P (260 mg, 0.990 mmol), and 4-bromo-2-fluorophenol (126 mg, 0.660 mmol) in tetrahydrofuran (2mL) to give a tan solution. DIAD (0.180 mL, 0.924 mmol) was added at rt. The resulted clear tan 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: ^{1}H 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.



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 Na_2CO_3 (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 (Na_2SO_4) 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: ^{1}H 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 $C_{24}H_{33}F_1N_3O_4$, 446.2]; LC/MS retention time (method B): t_R = 2.11 min.

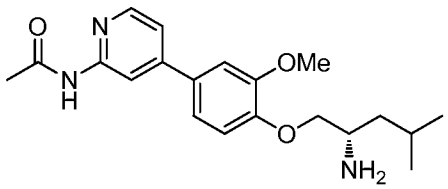


Part 2C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

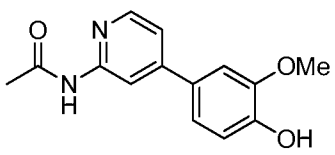
To a 50 mL round-bottomed flask was added (*S*)-*tert*-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-fluorophenoxy)-4-methylpentan-2-yl)carbamate (202 mg, 0.453 mmol) in dichloromethane (2 mL) to give a colorless solution. TFA (0.5 mL) was added, and the resulted tan solution was stirred at rt for 1 h. The 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 brine, dried (Na_2SO_4) 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: ^{1}H NMR and LCMS matched that of the material prepared above; ^{19}F NMR (376 MHz, Chloroform-d) δ -133.47.

Example 2

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

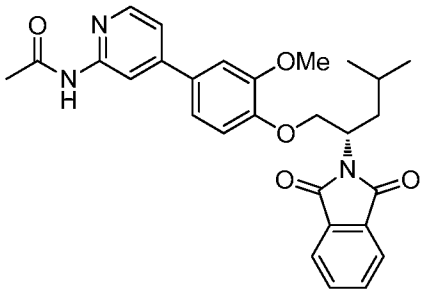


Prepared as described in Example 1.



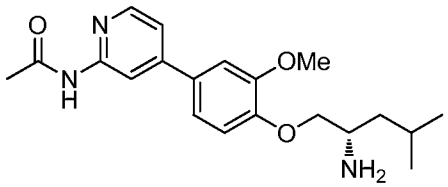
Part A: N-(4-(3-methoxy-4-hydroxyphenyl)pyridin-2-yl)acetamide

LCMS (ESI) *m/e* 259.1 [$(M+H)^+$, calcd $C_{14}H_{15}N_2O_3$, 259.3]; LC/MS retention time (method A): t_R = 1.51 min.



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

LCMS (ESI) *m/e* 488.3 [$(M+H)^+$, calcd $C_{28}H_{30}N_3O_5$, 488.2]; LC/MS retention time (method A): t_R = 2.17 min.

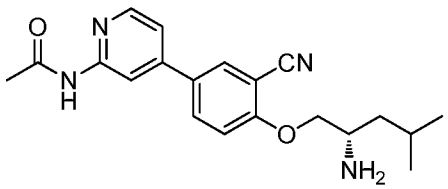


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide.

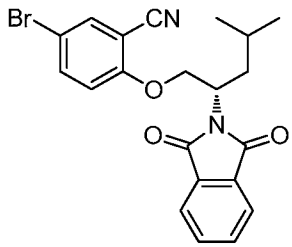
Obtained (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methoxyphenyl)pyridin-2-yl)acetamide (14.9 mg, 0.042 mmol, 80% yield for final step) as a slightly tan foam: ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.35 (s, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.32 - 7.22 (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 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 $C_{20}H_{28}N_3O_3$, 358.2]; LC/MS retention time (method A): t_R = 1.70 min.

Example 3

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

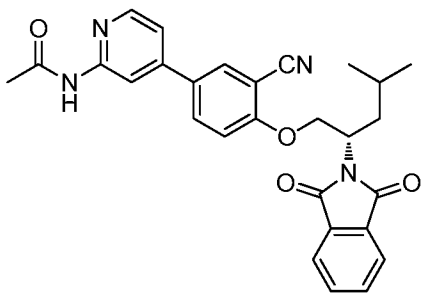


Prepared as described in Example 1.



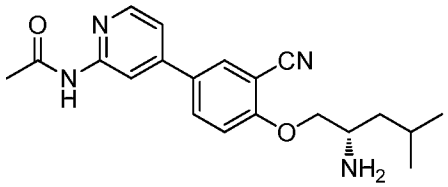
Part A: (S)-5-bromo-2-((2-(1,3-dioxoisoindolin-2-yl)-4-methylpentyl)oxy)benzonitrile.

^{1}H 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 $C_{21}H_{20}Br_1N_2O_3$, 427.1]; LC/MS retention time (method B): t_R = 2.29 min.



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

LCMS (ESI) *m/e* 483.3 [$(M+H)^+$, calcd $C_{28}H_{27}N_4O_4$, 483.2]; LC/MS retention time (method B): t_R = 2.06 min.

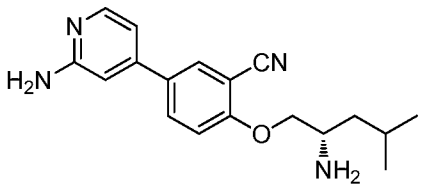


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide

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)-3-cyanophenyl)pyridin-2-yl)acetamide (10.1 mg, 0.028 mmol, 23% yield) as a colorless foam. ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{20}H_{25}N_4O_2$, 353.2]; LC/MS retention time (method B): t_R = 1.44 min.

Example 4

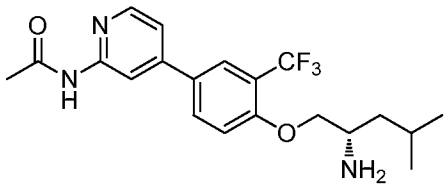
(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-aminopyridin-4-yl)benzonitrile



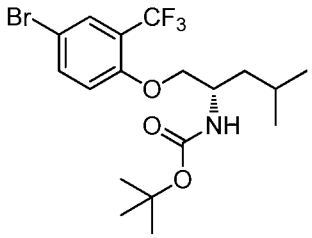
The hydrolyzed material from Example 3 was identified as (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-aminopyridin-4-yl)benzonitrile (10.1 mg, 0.030 mmol, 26% yield) as a colorless foam. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.02 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 5.3 Hz, 1H), 7.93 (dd, *J* = 8.8, 2.4 Hz, 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 $C_{18}H_{23}N_4O_1$, 311.2]; LC/MS retention time (method B): t_R = 1.35 min.

Example 5

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

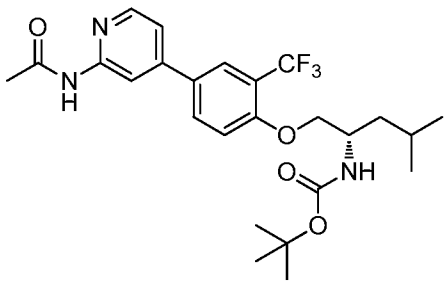


Prepared as described in Example 1.



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

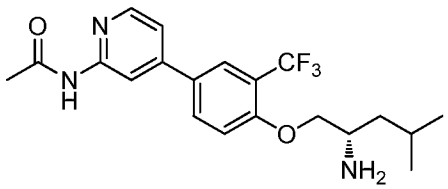
^{1}H NMR (400 MHz, Chloroform-d) δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.71 (d, *J* = 8.3 Hz, 1H), 4.03 (p, *J* = 7.2 Hz, 3H), 1.68 (hept, *J* = 6.7 Hz, 1H), 1.55 - 1.48 (m, 2H), 1.44 (s, 9H), 0.95 (dd, *J* = 6.6, 4.2 Hz, 6H); LCMS (ESI) *m/e* 462.1 [(M+Na)$^+$, calcd $C_{18}H_{25}Br_1F_3N_1Na_1O_3$, 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.

^{1}H 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 $C_{25}H_{33}F_3N_3O_4$, 446.2]; LC/MS retention time (method A): t_R = 2.28 min.

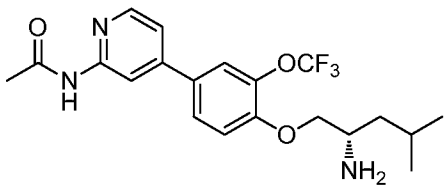


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

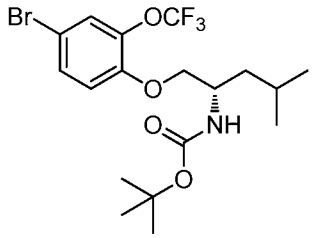
(221 mg, 0.531 mmol, quantitative yield for final step) as a white foam. ^{1}H NMR (400 MHz, Chloroform-d) δ 9.15 (s, 1H), 8.48 (s, 1H), 8.30 (d, *J* = 5.3 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.82 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.23 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 4.08 (dd, *J* = 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -62.40; LCMS (ESI) *m/e* 394.2 [$(M-H)^-$, calcd $C_{20}H_{23}F_3N_3O_2$, 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

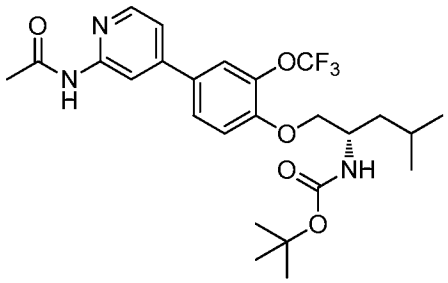


Prepared as described in Example 1.



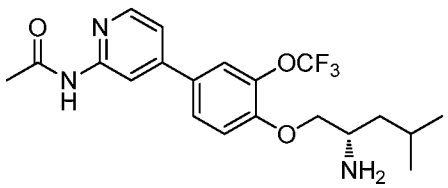
Part A: (S)-tert-butyl (1-(4-bromo-2-(trifluoromethoxy)phenoxy)-4-methylpentan-2-yl)carbamate.

^{1}H 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 $C_{18}H_{25}Br_1F_3N_1Na_1O_4$, 478.0]; LC/MS retention time (method B): t_R = 2.45 min.



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

^{1}H 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, 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 $C_{25}H_{33}F_3N_3O_5$, 512.2]; LC/MS retention time (method A): t_R = 2.29 min.

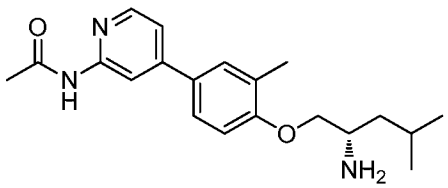


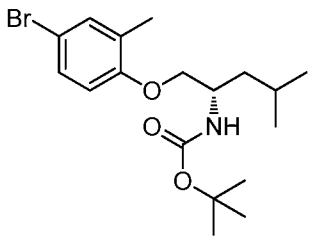
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide

(225 mg, 0.520 mmol, 95% yield for final step) as a white foam. ^{1}H 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), 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 [(M+H)$^+$, calcd $C_{20}H_{25}F_3N_3O_3$, 412.2]; LC/MS retention time (method A): t_R = 1.99 min.

Example 7

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

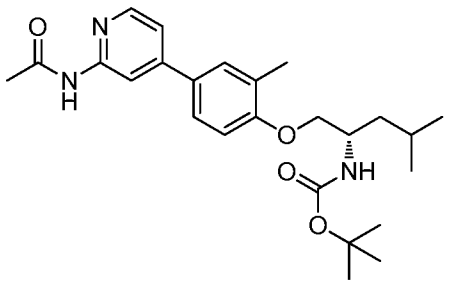




Part A: (S)-tert-butyl (1-(4-bromo-2-methylphenoxy)-4-methylpentan-2-yl)carbamate

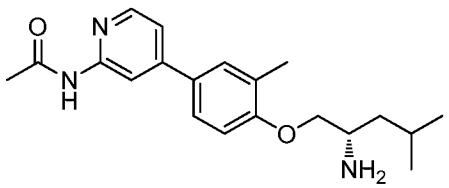
DIAD (0.090 mL, 0.464 mmol) was added to a solution of triphenylphosphine(0.097 g, 0.371 mmol), 4-bromo-2-methylphenol (0.069 g, 0.371 mmol) and (*S*)-*tert*-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (0.0672 g, 0.309 mmol) in THF (1.5 mL) at rt under N_2. The reaction was stirred at room temperature 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

(Na2SO4), 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 [$(M+Na)^+$, calcd $C_{18}H_{28}BrNO_3Na$, 408.1]; LC/MS retention time (method B): t_R = 2.44 min.



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), (*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. $PdCl_2$(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 diluted with ethyl acetate. The organic layer was separated and washed with brine (1X). The ethyl acetate layer was separated, dried (Na_2SO_4), 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 $C_{25}H_{36}N_3O_4$, 442.3]; LC/MS retention time (method B): t_R = 2.13 min.



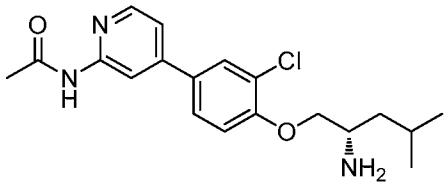
Part C: (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)acetamide

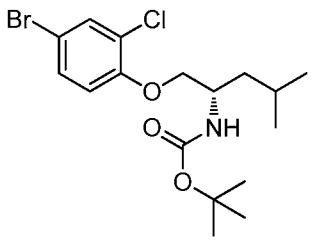
A mixture of TFA (1 mL, 12.98 mmol) and (*S*)-*tert*-butyl (1-(4-(2-acetamidopyridin-4-yl)-2-methylphenoxy)-4-methylpentan-2-yl)carbamate (35.8 mg,

0.081 mmol) in CH_2Cl_2 (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 mmol, 35% yield for two steps). ^{1}H NMR (500MHz, DMSO-d_6) 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* 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

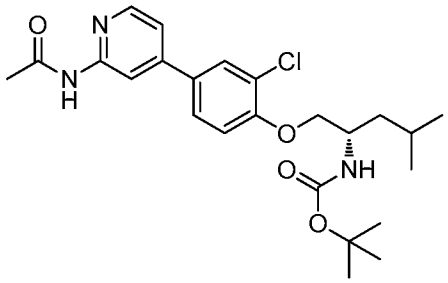
(*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)acetamide





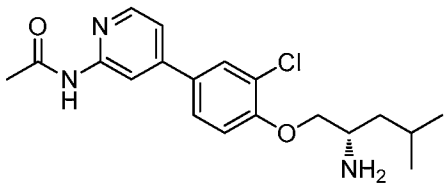
Part A: (S)-tert-butyl (1-(4-bromo-2-chlorophenoxy)-4-methylpentan-2-yl)carbamate

Prepared as described in Example 1, Part 2A. ^{1}H NMR (400MHz, 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.



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), (*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 N_2 (5X). $PdCl_2$(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 (Na_2SO_4), 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 $C_{24}H_{33}ClN_3O_4$, 462.2]; LC/MS retention time (method B): t_R = 2.21 min.



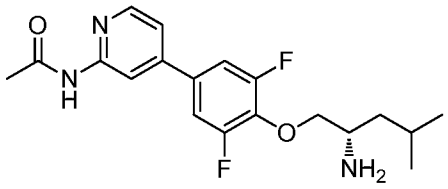
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)acetamide

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 mL, 12.98 mmol) was stirred in CH_2Cl_2 (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). ^{1}H NMR (500MHz, DMSO-d_6) δ 10.58 (br. s., 1H), 8.35 (d, *J*=4.6 Hz,

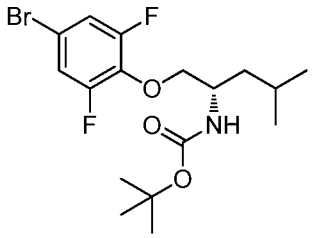
2H), 7.81 (s, 1H), 7.70 (d, *J*=8.9 Hz, 1H), 7.42 (d, *J*=5.2 Hz, 1H), 7.33 (d, *J*=8.5 Hz, 1H), 4.18 - 4.12 (m, 1H), 4.08 - 4.01 (m, 1H), 3.39 - 3.35 (m, 1H), 2.13 (s, 3H), 1.86 - 1.74 (m, 1H), 1.50 (d, *J*=6.1 Hz, 1H), 1.45 - 1.36 (m, 1H), 0.92 (dd, *J*=10.2, 6.6 Hz, 6H); LCMS (ESI) *m/e* 362.2 $[(M+H)^+$, calcd $C_{19}H_{25}ClN_3O_3$, 362.2]; LC/MS retention time (method B): t_R = 1.69 min.

Example 9

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

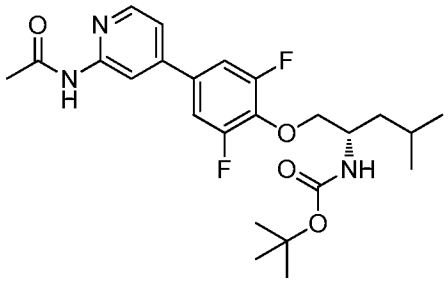


Prepared as described in Example 1.



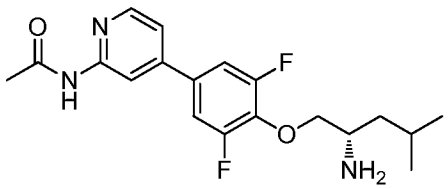
Part A: (S)-tert-butyl (1-(4-bromo-2,6-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

^{1}H 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 $C_{18}H_{25}Br_1F_3N_1Na_1O_4$, 478.0]; LC/MS retention time (method B): t_R = 2.45 min.



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

^{1}H 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 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 $C_{24}H_{32}F_2N_3O_4$, 464.2]; LC/MS retention time (method A): t_R = 2.24 min.

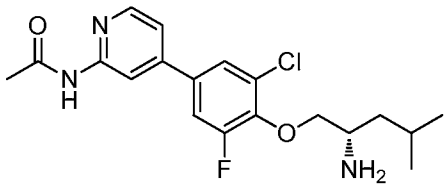


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide.

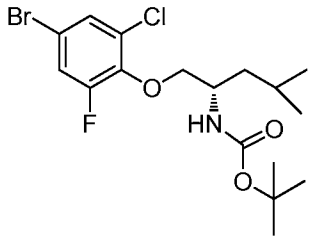
Obtained (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3,5-difluorophenyl)pyridin-2-yl)acetamide (48.4 mg, 0.152 mmol, 99% yield for final step) as an off-white foam. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.62 (s, 1H), 8.37 (d, *J* = 5.3 Hz, 1H), 8.32 (s, 1H), 7.59 - 7.48 (m, 2H), 7.42 (dd, *J* = 5.2, 1.8 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 $C_{19}H_{24}F_2N_3O_2$, 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

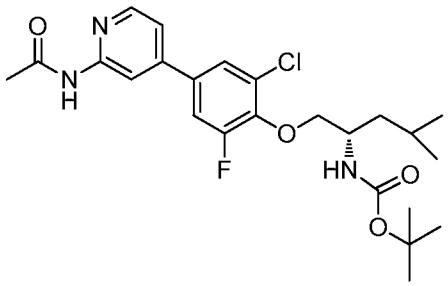


Prepared as described in Example 1.



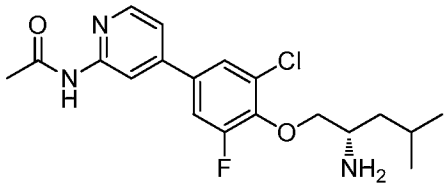
Part A: (S)-tert-butyl (1-(4-bromo-2,6-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

LCMS (ESI) *m/e* 424.2 [(M+H)$^+$, calcd $C_{17}H_{25}Br_1Cl_1F_1N_1O_3$, 424.1]; LC/MS 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.

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.

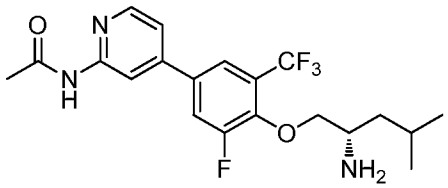


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide.

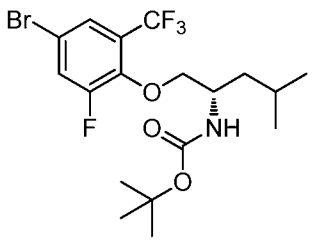
Obtained (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-3-chloro-5-fluorophenyl)pyridin-2-yl)acetamide (26.5 mg, 0.066 mmol, 56% yield for final step) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.60 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.30 (s, 1H), 7.67 (d, *J* = 9.5 Hz, 2H), 7.43 (d, *J* = 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), 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 $C_{19}H_{24}Cl_1F_1N_3O_2$, 380.2]; LC/MS retention time (method B): t_R = 1.82 min.

Example 11

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

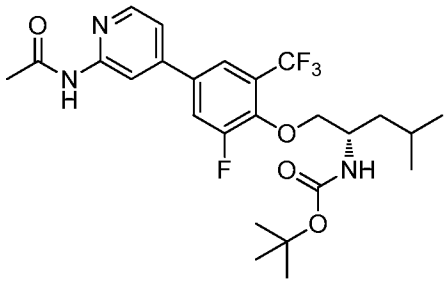


Prepared as described in Example 1.



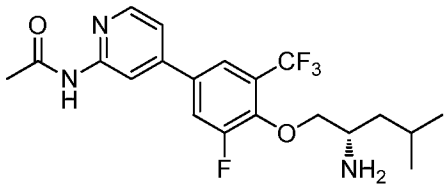
Part A: (S)-tert-butyl (1-(4-bromo-2-fluoro-6-(trifluoromethyl)phenoxy)-4-methylpentan-2-yl)carbamate.

^{1}H 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 $C_{18}H_{24}Br_1F_4N_1Na_1O_3$, 480.1]; LC/MS retention time (method B): t_R = 2.50 min.



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.



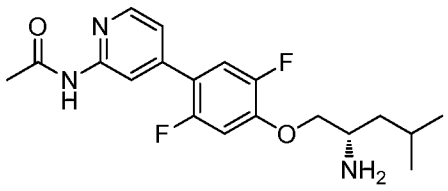
Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluoro-5-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide.

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. ^{1}H 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*

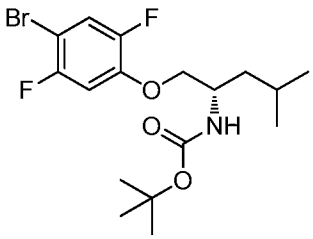
414.2 [(M+H)$^+$, calcd $C_{20}H_{24}F_4N_3O_2$, 414.2]; LC/MS retention time (method A): t_R = 2.01 min.

Example 12

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

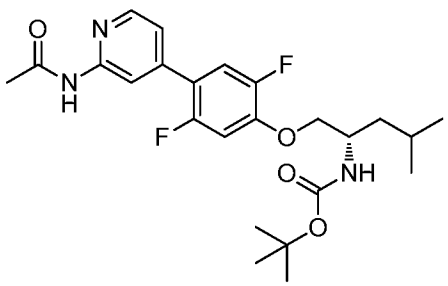


Prepared as described in Example 1.



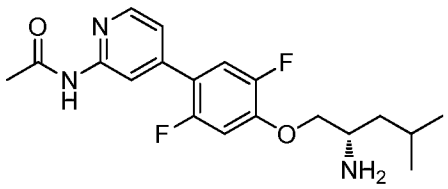
Part A: (S)-tert-butyl (1-(4-bromo-2,5-difluorophenoxy)-4-methylpentan-2-yl)carbamate.

^{1}H 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 $C_{17}H_{25}Br_1F_2N_1O_3$, 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 $C_{24}H_{32}F_2N_3O_4$, 464.3]; LC/MS retention time (method A): t_R = 2.29 min.

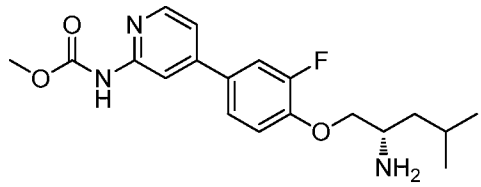


Part C: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide.

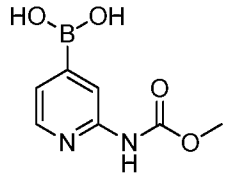
Obtained (*S*)-*N*-(4-(4-((2-amino-4-methylpentyl)oxy)-2,5-difluorophenyl)pyridin-2-yl)acetamide (46.4 mg, 0.125 mmol, 77% yield for final step) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.59 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.29 (s, 1H), 7.54 (dd, *J* = 11.8, 7.3 Hz, 1H), 7.34 (dd, *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

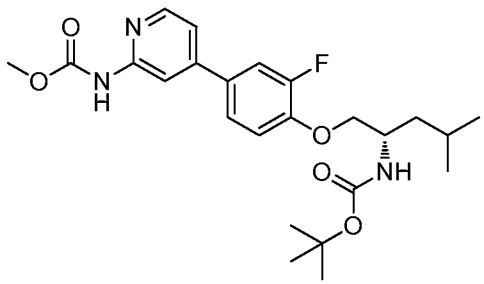


Prepared as described in Example 1.



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

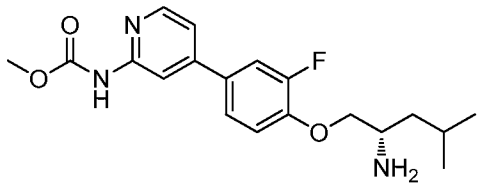
The mixture of 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl(0.079 g, 0.166 mmol), potassium acetate(2.446 g, 24.92 mmol), 2nd generation Xphos precatalyst (0.065 g, 0.083 mmol), methyl (4-chloropyridin-2-yl)carbamate (1.55 g, 8.31 mmol) and hypodiboric acid (1.117 g, 12.46 mmol) in ethanol (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.



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

^{1}H NMR (400 MHz, Chloroform-d) δ 9.86 (s, 1H), 8.35 (d, *J* = 5.4 Hz, 1H), 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 = 2.20 min.

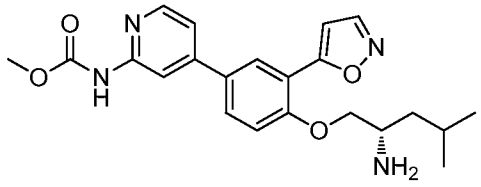


Part C: (S)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate.

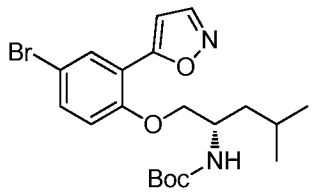
Obtained (*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate (33.2 mg, 0.091 mmol, 93% yield for the final step) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.30 (d, J = 5.3 Hz, 1H), 8.09 (s, 1H), 7.63 (dd, J = 12.7, 2.4 Hz, 1H), 7.55 - 7.49 (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, 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.

Example 14

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

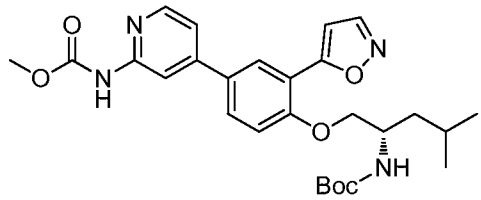


Prepared as described in Example 1.



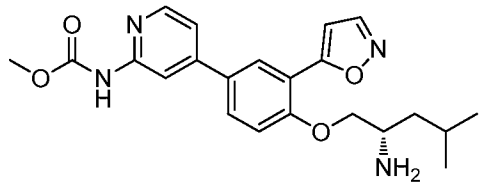
Part A: (S)-tert-butyl (1-(4-bromo-2-(isoxazol-5-yl)phenoxy)-4-methylpentan-2-yl)carbamate.

^{1}H 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.



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.



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

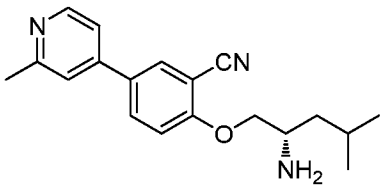
Obtained (*S*)-methyl (4-(4-((2-amino-4-methylpentyl)oxy)-3-(isoxazol-5-yl)phenyl)pyridin-2-yl)carbamate (10.9 mg, 0.027 mmol, 34% yield for the final step) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (d, *J* = 1.7 Hz, 1H), 8.34 (d, *J* = 5.2 Hz, 1H), 8.19 (t, *J* = 2.4 Hz, 2H), 7.89 (dd, *J* = 8.7, 2.4 Hz, 1H),

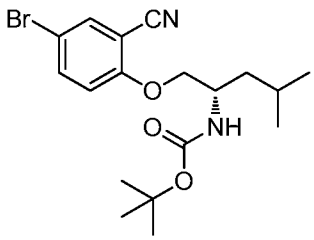
7.44 (d, *J* = 5.3 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 1.9 Hz, 1H), 4.18 (dd, *J* = 9.7, 4.5 Hz, 1H), 4.09 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.72 (s, 3H), 3.36 (d, *J* = 4.3 Hz, 1H), 1.83 (dt, *J* = 13.7, 6.7 Hz, 1H), 1.44 (dt, *J* = 13.6, 7.0 Hz, 1H), 1.41 - 1.32 (m, 1H), 0.92 (dd, *J* = 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

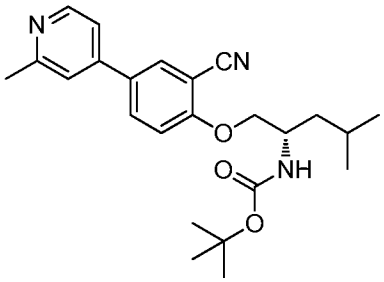
(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile

Prepared as described in Example 1.



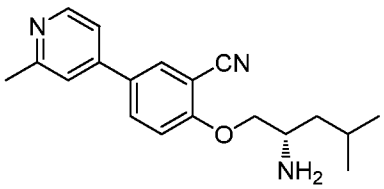


Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-4-methylpentan-2-yl)carbamate. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.68 (d, *J* = 2.5 Hz, 1H), 7.64 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 1H), 4.71 (s, 1H), 4.12 (t, *J* = 6.1 Hz, 1H), 4.10 - 3.98 (m, 2H), 1.79 - 1.67 (m, 1H), 1.59 (dd, *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 $C_{18}H_{26}Br_1N_2O_3$, 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.

^{1}H 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 $C_{24}H_{32}N_3O_3$, 410.2]; LC/MS retention time (method A): t_R = 2.18 min.

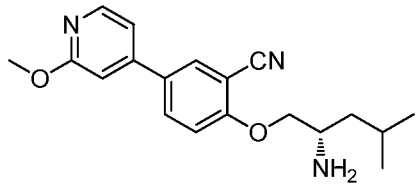


Part C: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile.

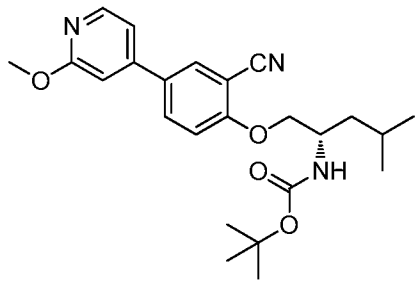
Obtained (48.4 mg, 0.152 mmol, 99% yield for the final step) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.49 (d, *J* = 5.3 Hz, 1H), 8.24 (d, *J* = 2.4 Hz, 1H), 8.11 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.65 (s, 1H), 7.57 - 7.52 (m, 1H), 7.38 (d, *J* = 8.9 Hz, 1H), 4.09 (dd, *J* = 9.5, 5.1 Hz, 1H), 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 $C_{19}H_{24}N_3O_1$, 310.2]; LC/MS retention time (method A): t_R = 1.82 min.

Example 16

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

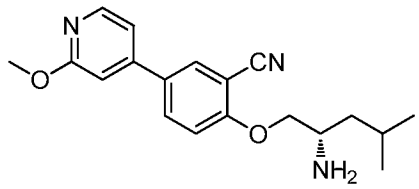


Prepared as described in Example 1.



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

^{1}H 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.



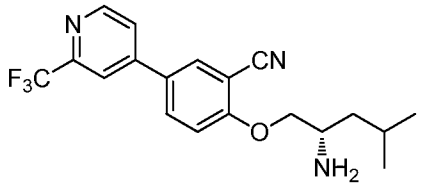
Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-methoxypyridin-4-yl)benzonitrile.

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. ^{1}H 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), 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,

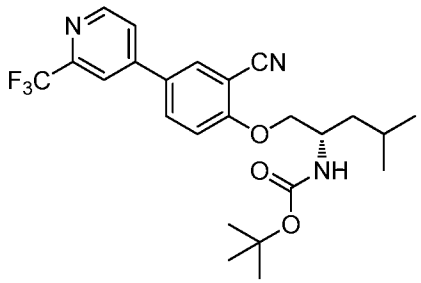
J = 13.3, 6.7 Hz, 1H), 1.36 (ddd, *J* = 13.4, 8.5, 4.9 Hz, 1H), 1.26 (ddd, *J* = 13.9, 8.8, 5.7 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); LCMS (ESI) *m/e* 326.1 [$(M+H)^+$, calcd $C_{19}H_{24}N_3O_2$, 326.2]; LC/MS retention time (method A): t_R = 1.88 min.

Example 17

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

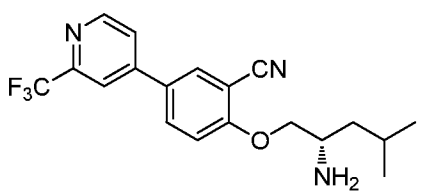


Prepared as described in Example 1.



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

^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -68.06; LCMS (ESI) *m/e* 486.2 [$(M+Na)^+$, calcd $C_{24}H_{28}F_3Na_1N_3O_3$, 486.2]; LC/MS retention time (method B): t_R = 2.35 min.

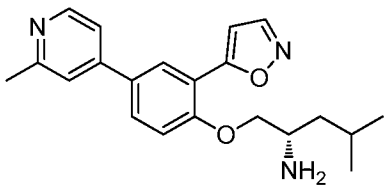


Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile.

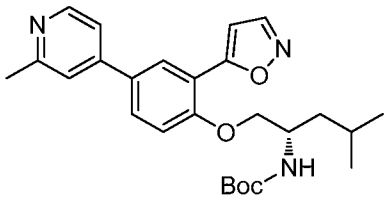
Obtained (*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(2-(trifluoromethyl)pyridin-4-yl)benzonitrile (34.3 mg, 0.093 mmol, 93% yield for the final step) as an off-white solid.. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.81 (d, *J* = 5.2 Hz, 1H), 8.46 (d, *J* = 2.9 Hz, 1H), 8.34 - 8.21 (m, 2H), 8.11 (d, *J* = 5.1 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 $C_{19}H_{21}F_3N_3O_1$, 364.2]; LC/MS retention time (method B): t_R = 1.97 min.

Example 18

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

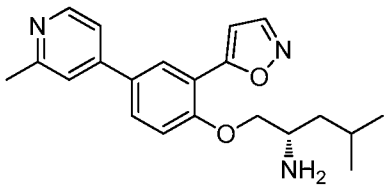


Prepared as described in Example 1.



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.

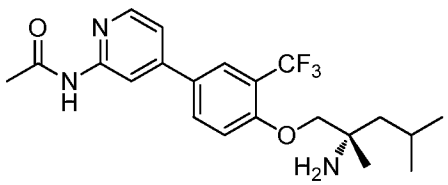


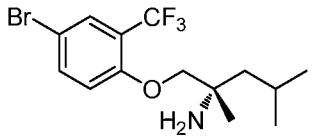
Part B: (S)-1-(2-(isoxazol-5-yl)-4-(2-methylpyridin-4-yl)phenoxy)-4-methylpentan-2-amine.

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. ^{1}H 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

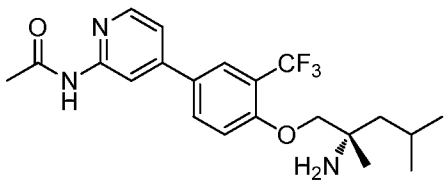




Part A: (S)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

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 (Na_2SO_4) and concentrated under reduced pressure to obtain crude (*S*)-1-(4-bromo-2-

(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (146 mg, o.412 mmol, 82% yield) as a tan oil which was used as is. ^{1}H 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); ^{19}F NMR (470 MHz, Chloroform-d) δ -62.61.; LCMS (ESI) *m/e* 354.0 [(M+H)$^+$, calcd $C_{14}H_{20}Br_1F_3N_1O_1$, 354.1]; LC/MS retention time (method B): t_R = 2.14 min.

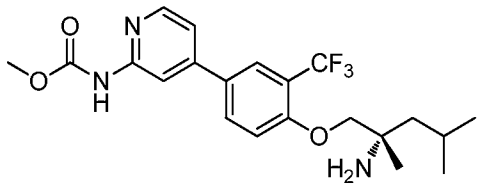


Part B: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)acetamide

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 Na_2CO_3 (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 Na_2SO_4. 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. ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{20}H_{23}F_3N_3O_2$, 410.2]; LC/MS retention time (method B): t_R = 1.87 min.

Example 20

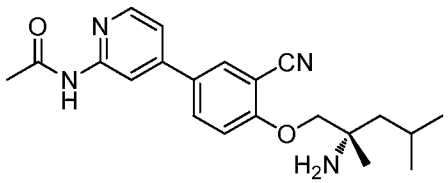
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)carbamate



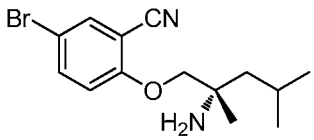
Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)carbamate (22.9 mg, 0.051 mmol, 38% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.29 (s, 1H), 8.32 (d, *J* = 5.3 Hz, 1H), 8.11 (s, 1H), 7.99 (d, *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 $C_{21}H_{27}F_3N_3O_3$, 426.2]; LC/MS retention time (method A): t_R = 2.23 min.

Example 21

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



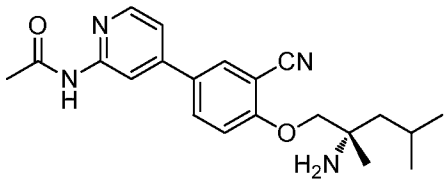
Prepared as described in Example 19



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

^{1}H 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 $C_{14}H_{20}BrN_2O$, 311.1]; LC/MS retention time (method A): t_R = 2.01 min.

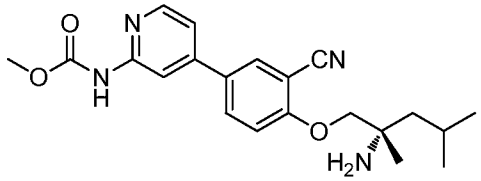


Part B: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)acetamide.

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. ^{1}H 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 $C_{21}H_{27}N_4O_2$, 367.2]; LC/MS retention time (method A): t_R = 1.82 min.

Example 22

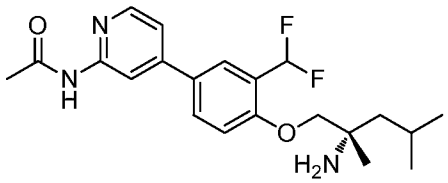
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)carbamate



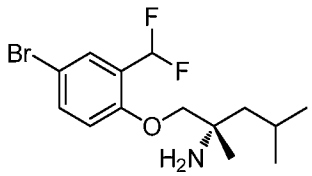
Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridin-2-yl)carbamate (21.1 mg, 0.053 mmol, 47% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.32 (d, J = 5.3 Hz, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 8.01 (d, 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 $C_{21}H_{26}N_4Na_1O_3$, 405.2]; LC/MS retention time (method B): t_R = 1.87 min.

Example 23

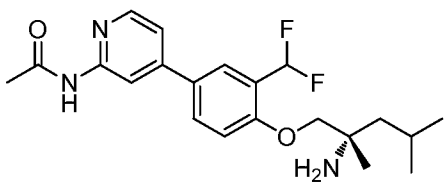
(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)acetamide



Prepared as described in Example 19.



Part A: (S)-1-(4-bromo-2-(difluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine. ^{1}H 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 [(M+H)$^+$, calcd $C_{14}H_{21}Br_1F_2N_1O_1$, 336.1]; LC/MS retention time (method A): t_R = 2.18 min.



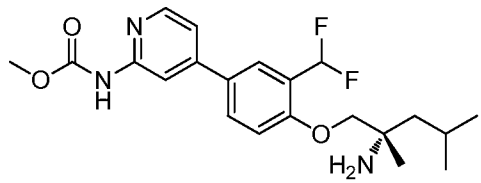
Part B: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)acetamide.

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. ^{1}H 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 [(M+H)$^+$, calcd $C_{21}H_{28}F_2N_3O_2$, 392.2]; LC/MS retention time (method A): t_R = 1.90 min.

Example 24

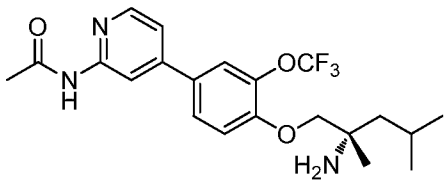
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)carbamate



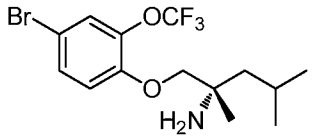
Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(difluoromethyl)phenyl)pyridin-2-yl)carbamate (15.4 mg, 0.037 mmol, 35% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 8.31 (d, *J* = 5.3 Hz, 1H), 8.11 (s, 1H), 7.91 - 7.85 (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 $C_{21}H_{28}F_2N_3O_3$, 408.2]; LC/MS retention time (method A): t_R = 2.00 min.

Example 25

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

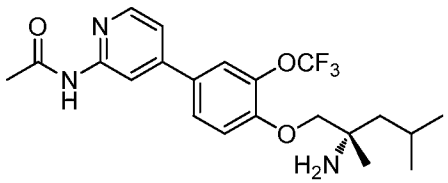


Prepared as described in Example 19.



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

^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -58.22; LCMS (ESI) *m/e* 370.1 [(M+H)$^+$, calcd $C_{14}H_{20}Br_1F_3N_1O_2$, 370.1]; LC/MS retention time (method A): t_R = 2.33 min.

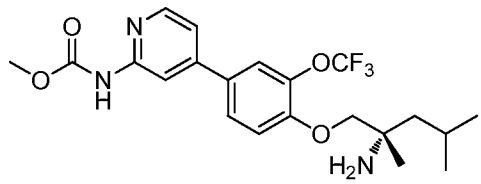


Part B: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)acetamide.

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. ^{1}H 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 $C_{21}H_{27}F_3N_3O_3$, 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

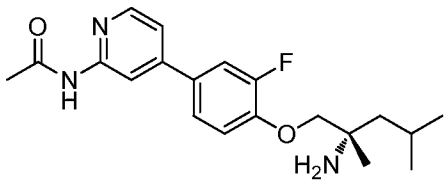


Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethoxy)phenyl)pyridin-2-yl)carbamate (11.5 mg, 0.026 mmol, 27% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 8.31 (d, *J* = 5.2 Hz, 1H), 8.10 (s, 1H), 7.75 (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);

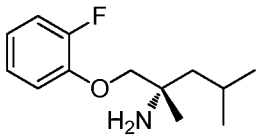
LCMS (ESI) *m/e* 442.2 [(M+H)$^+$, calcd $C_{21}H_{27}F_3N_3O_4$, 442.2]; LC/MS retention time (method B): t_R = 2.00 min.

Example 27

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

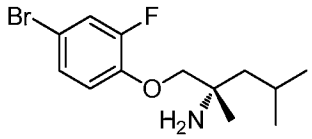


Prepared as described in Example 19.



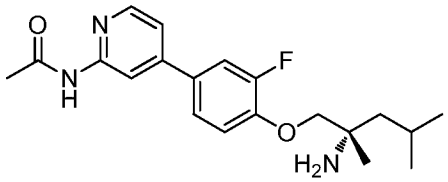
Part A: (S)-1-(2-fluorophenoxy)-2,4-dimethylpentan-2-amine.

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

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 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.

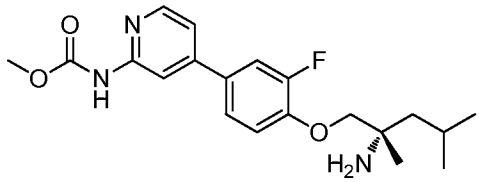


Part C: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide.

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. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.55 (s, 1H), 8.33 (d, *J* = 6.0 Hz, 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 = 1.82 min.

Example 28

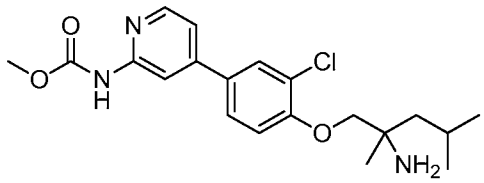
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate

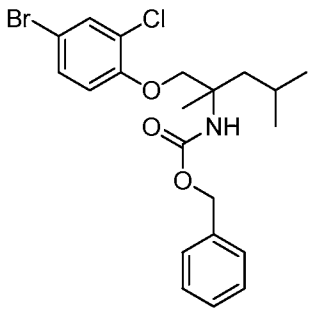


Prepared as described in Example 19 to obtain (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)carbamate (17.1 mg, 0.044 mmol, 30% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.25 (s, 1H), 8.29 (d, *J* = 5.3 Hz, 1H), 8.09 (s, 1H), 7.62 (d, *J* = 12.4 Hz, 1H), 7.53 (d, *J* = 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.

Example 29

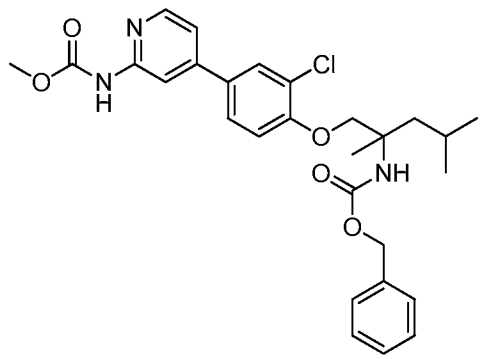
methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate





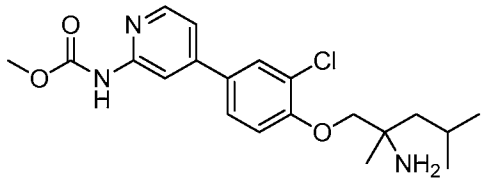
Part A: Benzyl (1-(4-bromo-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate

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-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 (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was carried on without further purification. LCMS (ESI) *m/e* 476.1 [$(M+Na)^+$, calcd $C_{21}H_{25}BrClNaNO_3$, 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'-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) 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 (Na_2SO_4), 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 $C_{28}H_{32}ClN_3O_5Na$, 548.2]; LC/MS retention time (method B): t_R = 2.25 min.



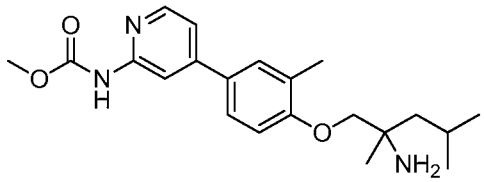
Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridin-2-yl)carbamate

Triethylsilane(0.026 mL, 0.161 mmol) was added to a CH_2Cl_2 (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 CH_2Cl_2 (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 CH_2Cl_2 (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 nM 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-

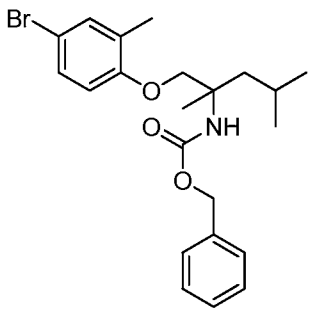
white solid. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.27 (br. s., 1H), 8.30 (d, *J*=5.2 Hz, 1H), 8.08 (s, 1H), 7.79 (s, 1H), 7.68 (d, *J*=8.2 Hz, 1H), 7.37 (d, *J*=5.2 Hz, 1H), 7.26 (d, *J*=8.5 Hz, 1H), 3.82 (d, *J*=2.4 Hz, 2H), 3.70 (s, 3H), 1.85 - 1.77 (m, 1H), 1.42 (br. s., 2H), 1.14 (s, 3H), 0.92 (m, 6H); LCMS (ESI) *m/e* 392.2 $[(M+H)^+$, calcd $C_{20}H_{27}ClN_3O_3$, 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

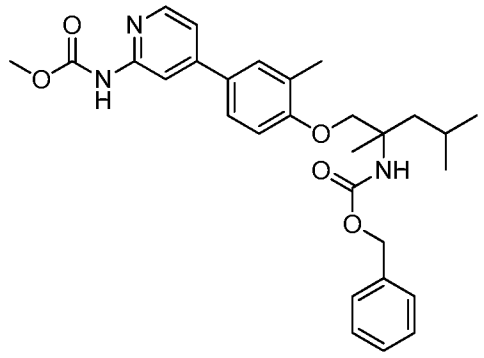


Prepared as described in Example 29.



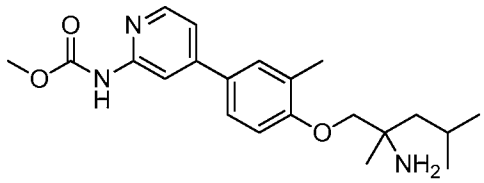
Part A: Benzyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate.

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.



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.

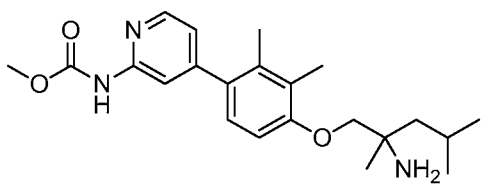


Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate.

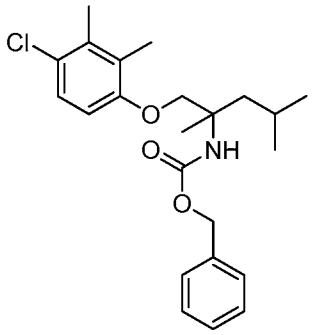
Obtained methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyridin-2-yl)carbamate (3.7 mg, 9.96 umol, 35% yield) as an off white solid. ^{1}H NMR (600MHz, DMSO-d_6) δ 10.11 (br. s., 1H), 8.26 (d, *J*=5.1 Hz, 1H), 8.08 (s, 1H), 7.53 (br. s., 2H), 7.34 - 7.27 (m, 1H), 7.03 (d, *J*=9.2 Hz, 1H), 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 $C_{21}H_{30}N_3O_3$, 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

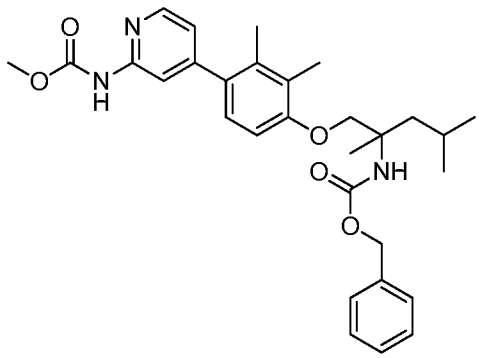


Prepared as described in Example 29.



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

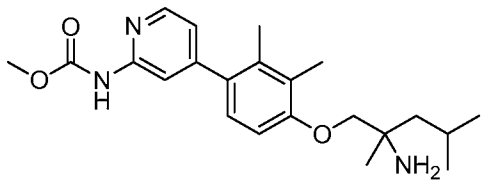
LCMS (ESI) *m/e* 426.3 [(M+Na)$^+$, calcd $C_{22}H_{29}ClN_2O_3Na$, 427.2]; LC/MS retention time (method B): t_R = 2.57 min.



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 µmol), potassium 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 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 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.

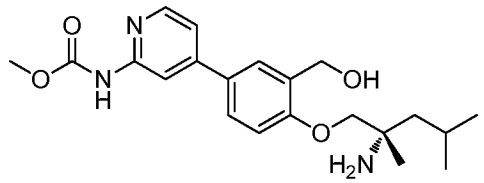


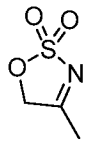
Part C: methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,3-dimethylphenyl)pyridin-2-yl)carbamate

A mixture of Pd/C (6 mg, 5.64 μmol) 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 H_2 balloon at room temperature overnight. The reaction mixture was filtered through a diatomaceous earth (Celite®) pad and washed with CH_2Cl_2. 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 umol, 15% yield) as an off-white solid. ^{1}H NMR (600MHz, DMSO-d_6) 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 [$(M-NH_2)^-$, calcd $C_{22}H_{29}N_2O_3$, 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

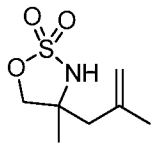




Part A. 4-methyl-5H-1,2,3-oxathiazole 2,2-dioxide

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 N_2, 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.

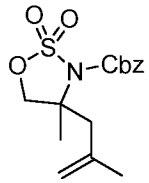
Step 2: In a separate 5L 4 neck reaction flask was charged hydroxyacetone (72.5 mL, 953 mmol), pyridine (116 mL, 1430 mmol), and DCM (2000 mL). This solution was cooled to -5°C under N_2. The sulfamoyl chloride solution was added slowly via Teflon tube over 10 min. After the addition, the reaction was stirred for 15 min then the ice bath was removed and the reaction mixture allowed to warm to 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. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 5.09 (s, 2H), 2.44 (s, 3H); LCMS (ESI) *m/e* 136.0 [$(M+H)^+$, calcd for $C_3H_6NO_3S$ 136.0].



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-5*H*-1,2,3-oxathiazole 2,2-dioxide (0.541 g, 4mmol) 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 NH_4Cl (50 mL) and EtOAc (20 mL) was added. The organic phase was separated, washed with brine (50 mL), dried over Na_2SO_4, 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 $C_7H_{14}NO_3S$ 192.1].



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

To a N_2 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 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 (50 mL), dried over Na_2SO_4, 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), 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,

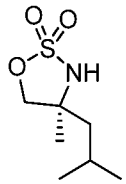
J=14.1 Hz, 1H), 1.78 (br. s, 3H), 1.64 (s, 3H); LCMS (ESI) *m/e* 326.1 [$(M+H)^+$, calcd for $C_{15}H_{20}NO_5S$ 326.1].

The racmeic compounds was separated by chiral super critical fluid chromatography (Column: OJ-H (3x25cm, 5µm); Mobile Phase: CO_2/ MeOH (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: CO_2/ MeOH (90/10); Detector Wavelength: UV 200-400nm

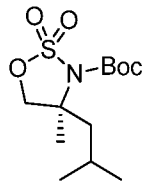
Enantiomer 1: (*S*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 2.53 min.

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



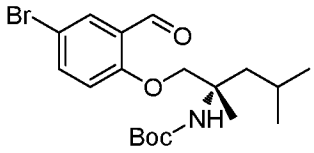
Part D. (S)-4-isobutyl-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide

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 was passed through diatomaceous earth (Celite®) pad and the 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. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.69 (br, 1H) 4.33 (d, J=8.03 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).



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

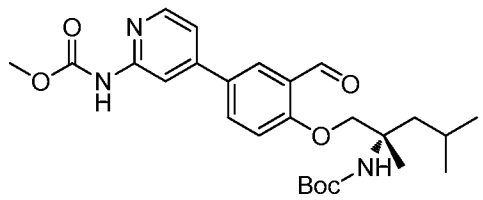
To a stirred solution of (*S*)-4-isobutyl-4-methyl-1,2,3-oxathiazolidine 2,2-dioxide (7 g, 15.21 mmol) in DCM (70 mL) cooled to 0 °C was added DMAP (1.858 g, 15.21 mmol) and $(BOC)_2O$ (5.30 mL, 22.82 mmol) The reaction mixture was stirred at rt for 12 h. The reaction mixture was transfers to a separating funnel 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 (Na_2SO_4), 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. ^{1}H 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), 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.

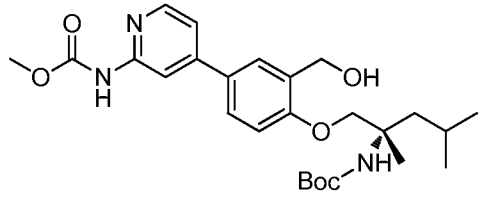
To a 20 mL vial was added 5-bromo-2-hydroxybenzaldehyde (81 mg, 0.403 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (107.4 mg, 0.366 mmol), and K_2CO_3 (152 mg, 1.098 mmol) in DMF (1.2 mL) to give a white suspension. The vial was sealed and the mixture was heated at 80 °C for 17 h. The reaction mixture was cooled to rt and partitioned between water and EtOAc. The layers were separated. The organic layer was washed with water, brine, dried (Na_2SO_4) 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. ^{1}H NMR (400 MHz, Chloroform-d) δ 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 $C_{14}H_{21}BrNO_2$, 414.1]; LC/MS retention time (method B): t_R = 2.39 min.



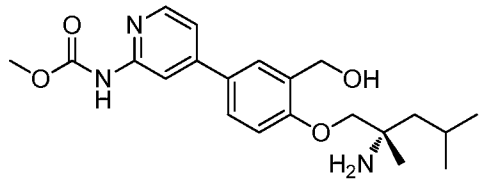
Part G: (S)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-carbonylphenyl)pyridin-2-yl)carbamate.

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-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (19.79 mg, 0.101 mmol), and Na_2CO_3 (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 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 Na_2SO_4. 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 residue which was carried on without further purification. LCMS (ESI) *m/e* 486.4 [(M+H)$^+$, calcd $C_{26}H_{36}N_3O_6$, 486.3]; LC/MS retention time (method C): t_R = 4.23 min.



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. $NaBH_4$ (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 layers were separated. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure . The tan residue was directly carried onto next reaction. LCMS (ESI) *m/e* 488.2 [$(M+H)^+$, calcd $C_{26}H_{38}N_3O_6$, 488.3]; LC/MS retention time (method B): t_R = 2.00 min.

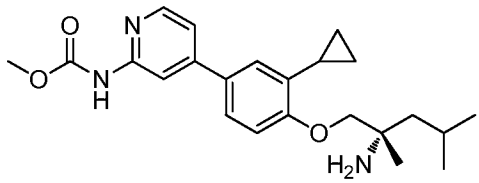


Part I: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl)carbamate

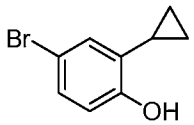
To a 25 mL flask was added (*S*)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-(hydroxymethyl)phenyl)pyridin-2-yl)carbamate (10.73 mg, 0.022 mmol) in CH_2Cl_2 (1 mL) to give a tan solution. TFA (0.5 ml, 6.49 mmol) was added under nitrogen. The mixture was stirred at rt for 1 h. The mixture was 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-d_6) 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 $C_{21}H_{30}N_3O_4$, 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

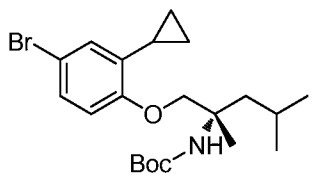


Prepared as described in Example 32.



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

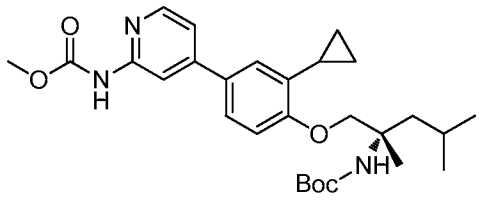
To a 100 mL round-bottomed flask was added 2-cyclopropylphenol (584 mg, 4.35 mmol) in CH_2Cl_2 (22 mL) to give a colorless solution. Br_2 (0.224 mL, 4.35 mmol) was added dropwise at 0°C. The mixture was stirred at 0 °C for 1 h. The mixture was concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-bromo-2-cyclopropylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (992 mg, 4.35 mmol, 100% yield) as a colorless oil. ^{1}H 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.

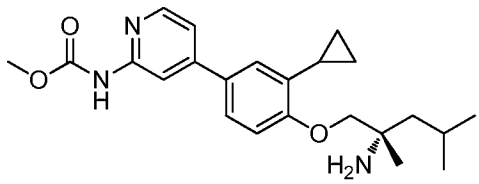
^{1}H NMR (400 MHz, Chloroform-d) δ 7.21 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.67 (s, 1H), 4.10 (d, *J* = 9.0 Hz, 1H), 3.94 (d, *J* = 8.8 Hz, 1H), 2.16 - 2.08 (m, 1H), 1.84 (ddt, *J* = 13.0, 10.9, 6.5 Hz, 2H), 1.69 -

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 $C_{21}H_{32}Br_1N_1Na_1O_3$, 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 $C_{28}H_{40}N_3O_5$, 498.3]; LC/MS retention time (method B): t_R = 2.24 min.

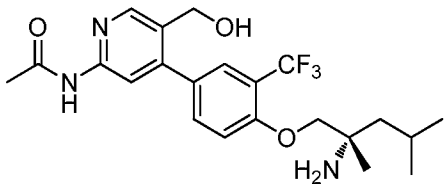


Part D: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyclopropylphenyl)pyridin-2-yl)carbamate.

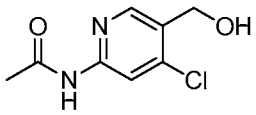
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (d, *J* = 5.3 Hz, 1H), 8.05 (s, 1H), 7.50 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.19 (d, *J* = 2.3 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 3.81 - 3.73 (m, 2H), 3.70 (s, 3H), 2.20 (ddd, *J* = 13.9, 8.8, 5.4 Hz, 1H), 1.82 (dt, *J* = 12.8, 6.3 Hz, 1H), 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 $C_{23}H_{32}N_3O_3$, 398.2]; LC/MS retention time (method B): t_R = 1.73 min.

Example 34

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

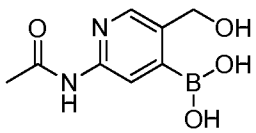


Prepared as described in Example 19.



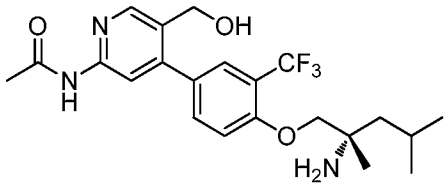
Part A: *N*-(4-chloro-5-(hydroxymethyl)pyridin-2-yl)acetamide

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 N_2, $PdOAc_2$ (7.93 mg, 0.035 mmol), XANTPHOS (30.7 mg, 0.053 mmol), Cs_2CO_3 (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 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/CH_2Cl_2) to afford *N*-(4-chloro-5-(hydroxymethyl)pyridin-2-yl)acetamide (90 mg, o.449 mmol, 64% yield) as a white solid: ^{1}H NMR (400 MHz, Methanol-d_4) 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 $C_8H_{10}ClN_2O_2$, 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 N_2 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.

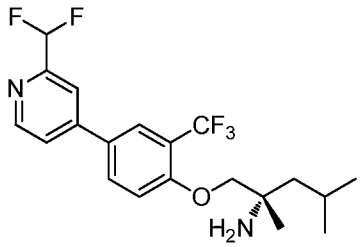


Part C: (S)-N-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-5-(hydroxymethyl)pyridin-2-yl)acetamide

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 N_2 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. ^{1}H 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 $C_{22}H_{29}F_3N_3O_3$, 440.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 35

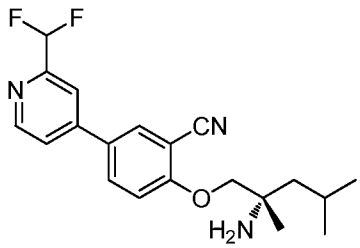
(*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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 $C_{20}H_{24}F_5N_2O_1$, 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

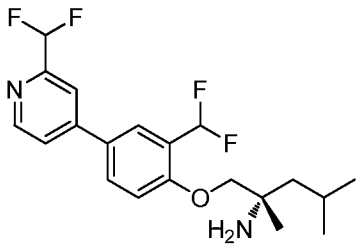


Prepared as described in Example 19. Obtained (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyridin-4-yl)benzonitrile (32 mg, 0.086 mmol, 60% yield) as an off-white solid.. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.11 (d, *J* = 2.5 Hz, 1H), 7.95 (dd, *J* = 9.0, 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 - 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -115.30 (d,

J = 54.0 Hz); LCMS (ESI) m/e 360.2 [$(M+H)^+$, calcd $C_{20}H_{24}F_2N_3O_1$, 360.2]; LC/MS retention time (method B): t_R = 1.69 min.

Example 37

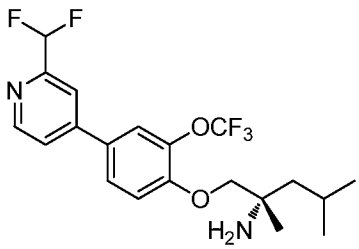
(*S*)-1-(2-(difluoromethyl)-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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-d6) δ -73.65 , -115.33; LCMS (ESI) m/e 407.2 [$(M+Na)^+$, calcd $C_{20}H_{24}F_4N_2Na_1O_1$, 407.2]; LC/MS retention time (method B): t_R = 1.89 min.

Example 38

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

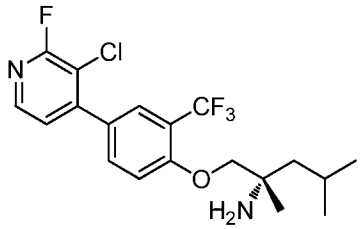


Prepared as described in Example 19. Obtained (*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2-(trifluoromethoxy)phenoxy)-2,4-dimethylpentan-2-amine (21.1 mg, 0.050 mmol, 39% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 5.2 Hz, 1H), 7.85 (s, 1H), 7.78 (dd, J = 13.4, 5.4 Hz, 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 [$(M+H)^+$, calcd $C_{20}H_{24}F_5N_2O_2$, 419.2]; LC/MS retention time (method B): t_R = 2.03 min.

Example 39

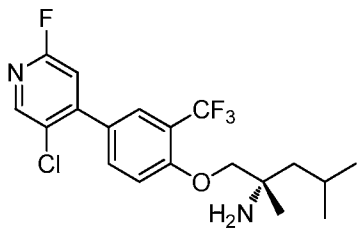
(*S*)-1-(4-(3-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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 = 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 $C_{19}H_{22}Cl_1F_4N_2O_1$, 405.1]; LC/MS retention time (method B): t_R = 2.04 min.

Example 40

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

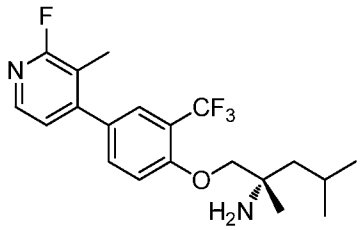


Prepared as described in Example 19. Obtained (*S*)-1-(4-(5-chloro-2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (15.2 mg, 0.037 mmol, 43% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ

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-d6) δ -61.16 , -71.37; LCMS (ESI) *m/e* 405.1 [(M+H)$^+$, calcd $C_{19}H_{22}Cl_1F_4N_2O_1$, 405.1]; LC/MS retention time (method B): t_R = 2.04 min.

Example 41

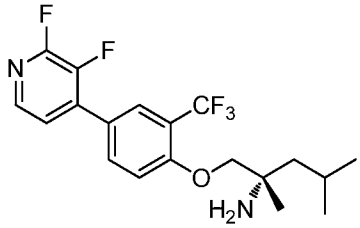
(*S*)-1-(4-(2-fluoro-3-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 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-d6) δ -61.03 , -71.80; LCMS (ESI) *m/e* 385.2 [(M+H)$^+$, calcd $C_{20}H_{25}F_4N_2O_1$, 385.2]; LC/MS retention time (method B): t_R = 1.99 min.

Example 42

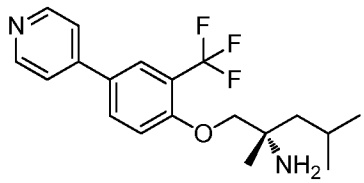
(*S*)-1-(4-(2,3-difluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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-d6) δ -61.23 , -89.72 , -89.79; LCMS (ESI) *m/e* 389.2 [(M+H)$^+$, calcd $C_{19}H_{22}F_5N_2O_1$, 389.2]; LC/MS retention time (method B): t_R = 2.01 min.

Example 43

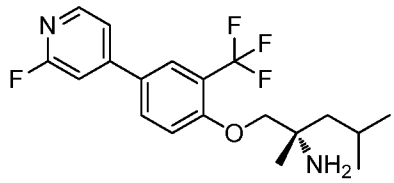
(*S*)-2,4-dimethyl-1-(4-(pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine



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 N_2) 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 (Na_2SO_4), 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. ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{19}H_{24}F_3N_2O$, 353.2]; LC/MS retention time (method B): t_R = 1.48 min.

Example 44

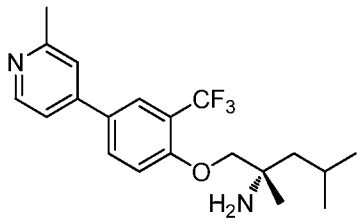
(*S*)-1-(4-(2-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (400MHz, METHANOL-d$_4$) 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 $C_{19}H_{23}F_4N_2O$, 371.2]; LC/MS retention time (method B): t_R = 1.95 min.

Example 45

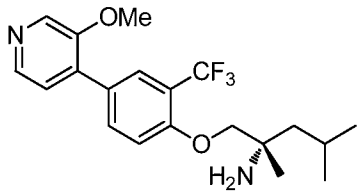
(*S*)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine



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. ^{1}H 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), 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-d6) δ -60.51, -73.76 (TFA); LCMS (ESI) *m/e* 367.2 [(M+H)$^+$, calcd $C_{20}H_{26}F_3N_2O_1$, 367.2]; LC/MS retention time (method B): t_R = 1.51 min.

Example 46

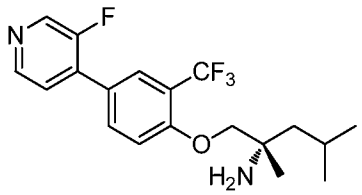
(*S*)-1-(4-(3-methoxypyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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); ^{19}F NMR (376 MHz, DMSO-d$_6$) δ -61.00; LCMS (ESI) *m/e* 383.2 [(M+H)$^+$, calcd $C_{20}H_{26}F_3N_2O_2$, 383.2]; LC/MS retention time (method B): t_R = 1.58 min.

Example 47

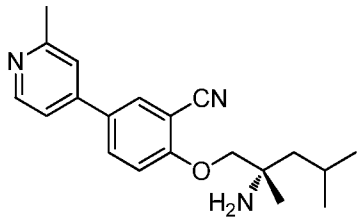
(*S*)-1-(4-(3-fluoropyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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), 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -61.17 , -133.88; LCMS (ESI) *m/e* 371.2 [(M+H)$^+$, calcd $C_{19}H_{23}F_4N_2O_1$, 371.2]; LC/MS retention time (method B): t_R = 1.88 min.

Example 48

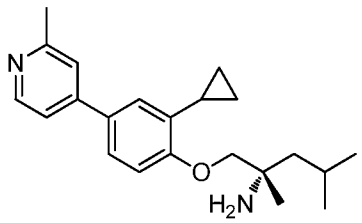
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methylpyridin-4-yl)benzonitrile



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. ^{1}H 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 $C_{20}H_{26}N_3O_1$, 324.2]; LC/MS retention time (method B): t_R = 1.46 min.

Example 49

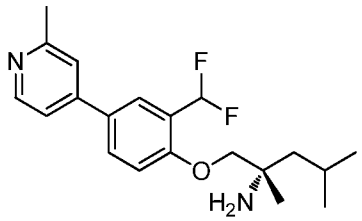
(*S*)-1-(2-cyclopropyl-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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 $C_{22}H_{31}N_2O_1$, 339.2]; LC/MS retention time (method B): t_R = 1.56 min.

Example 50

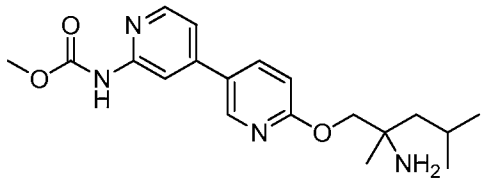
(*S*)-1-(2-(difluoromethyl)-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



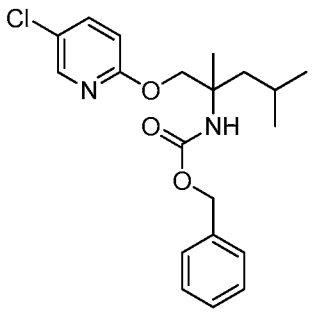
Prepared as described in Example 19. Obtained (*S*)-1-(2-(difluoromethyl)-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (22 mg, 0.061 mmol, 69% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.96 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 2.4 Hz, 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 $C_{20}H_{27}F_2N_2O_1$, 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



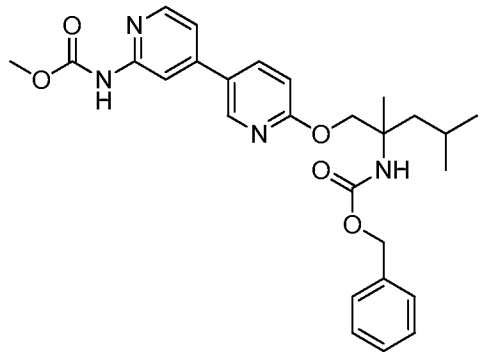
Prepared as described in Example 29.



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), sodium carbonate (0.019 g, 0.180 mmol) and benzyl 4-isobutyl-4-methyl-1,2,3-

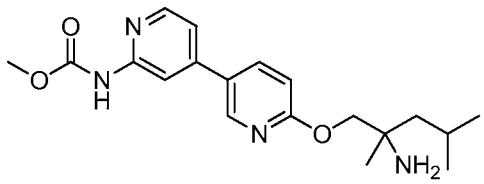
oxathiazolidine-3-carboxylate 2,2-dioxide (0.0392 g, 0.120 mmol) was heated to 80 °C overnight. The reaction mixture was cooled to rt and diluted with ethyl acetate and washed with water (3X). The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified via silica 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. ^{1}H 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, 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 $C_{20}H_{26}ClN_2O_3$, 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

A mixture of 2nd generation XPHOS precatalyst (1.587 mg, 2.017 μmol), 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/ N_2 fill cycle three times. 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 (Na_2SO_4), 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 $C_{27}H_{33}N_4O_5$, 493.3]; LC/MS retention time (method B): t_R = 2.13 min.

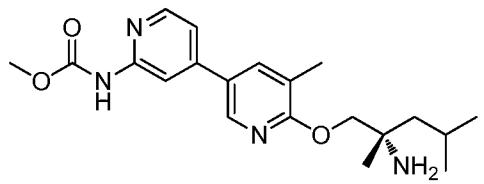


Part C: methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate

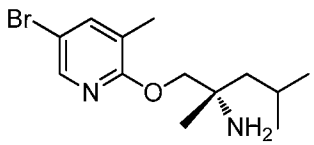
A mixture of Pd/C (5 mg, 4.70 µmol) and Cbz methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-[3,4'-bipyridin]-2'-yl)carbamate (0.011 g, 0.022 mmol) in ethanol (4 mL) was hydrogenated with a H_2 balloon at room temperature overnight. The reaction was filtered and washed with DCM. The filtrate was concentrated 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. ^{1}H NMR (600MHz, DMSO-d_6) 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 $C_{19}H_{27}N_4O_3$, 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

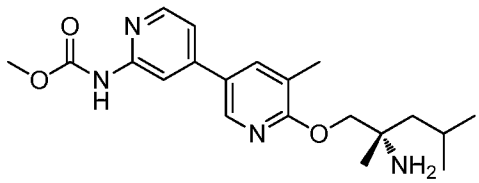


Prepared as in Example 51.



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 $C_{13}H_{21}BrN_2ONa$, 323.1]; LC/MS retention time (method B): t_R = 1.96 min.

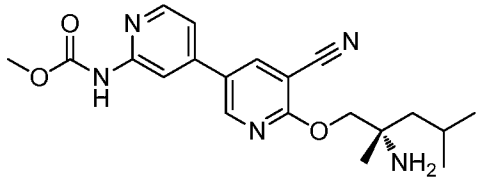


Part B: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methyl-[3,4'-bipyridin]-2'-yl)carbamate.

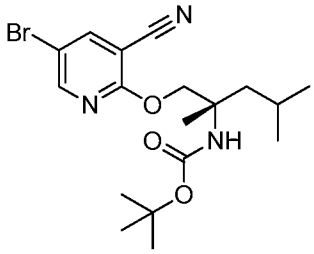
A mixture of sodium carbonate (0.149 mL, 0.299 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride dichloromethane complex (6.10 mg, 7.47 µmol), (*S*)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.045 g, 0.149 mmol) and (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.029 g, 0.149 mmol) in dioxane (0.5 mL) (degassed with N_2) 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 (Na_2SO_4), 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. ^{1}H NMR (600MHz, DMSO-d_6) 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 $C_{20}H_{29}N_4O3$ 373.2]; LC/MS retention time (method A): t_R = 1.89 min.

Example 53

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

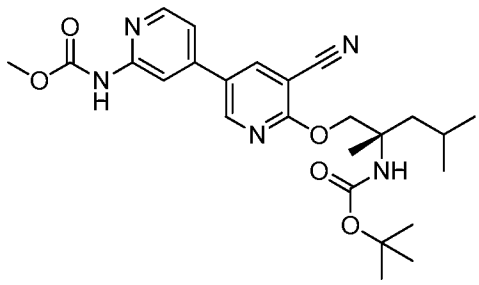


Prepared as in Example 51.



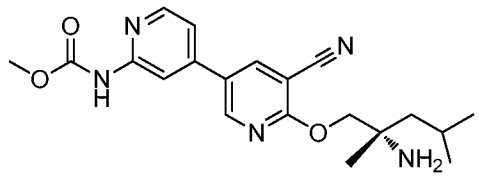
Part A: (*S*)-*tert*-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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 (Na_2SO_4), 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 $C_{18}H_{26}BrN_3O_3Na$, 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 $C_{25}H_{34}N_5O_5$, 484.3]; LC/MS retention time (method A): t_R = 2.24 min.

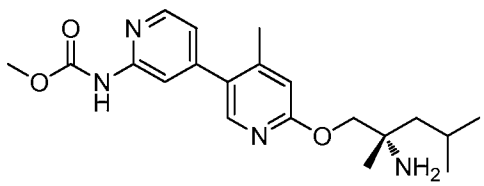


Part C: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate.

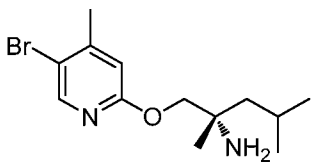
Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-cyano-[3,4'-bipyridin]-2'-yl)carbamate (13.3 mg, 0.034 mmol, 36% yield) as a white solid. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.36 (s, 1H), 8.81 - 8.77 (m, 1H), 8.68 - 8.63 (m, 1H), 8.36 (d, *J*=5.1 Hz, 1H), 8.09 (s, 1H), 7.43 (d, *J*=4.0 Hz, 1H), 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 $C_{20}H_{23}N_4O3$, 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

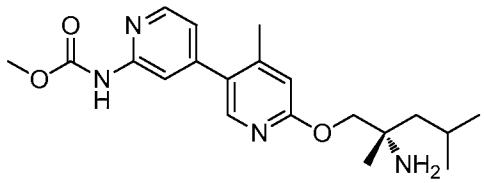


Prepared as in Example 51.



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 $C_{13}H_{22}BrN_2O$, 301.1]; LC/MS retention time (method A): t_R = 1.77 min.

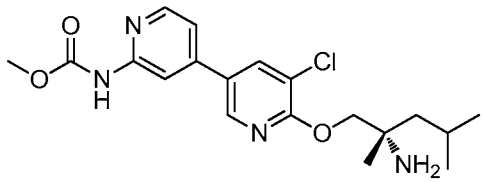


Part B: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate.

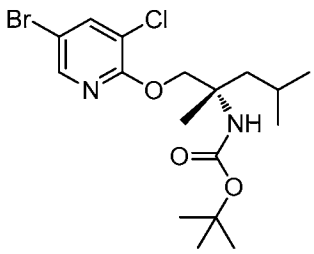
Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[3,4'-bipyridin]-2'-yl)carbamate (15.3 mg, 0.041 mmol, 32% yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.34 - 8.30 (m, 1H), 8.00 (s, 1H), 7.81 (s, 1H), 7.11 - 7.08 (m, 1H), 6.85 (s, 1H), 4.01 (d, *J*=5.5 Hz, 2H), 3.68 (s, 3H), 2.26 (s, 3H), 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 $C_{20}H_{29}N_4O3$, 373.2]; LC/MS retention time (method B): t_R = 1.60 min.

Example 55

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

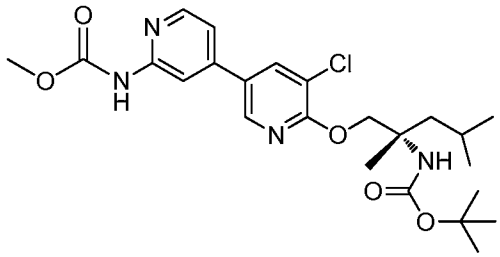


Prepared as in Example 51.



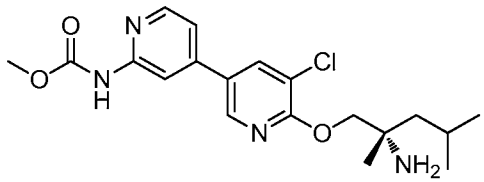
Part A: (S)-tert-butyl (1-((5-bromo-3-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

^{1}H 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.



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 $C_{24}H_{34}ClN_4O_5$, 493.2]; LC/MS retention time (method A): t_R = 2.38 min.

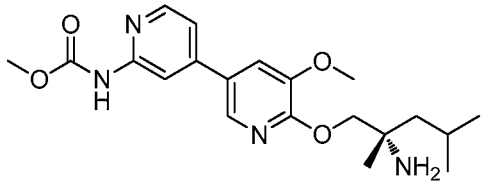


Part C: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate.

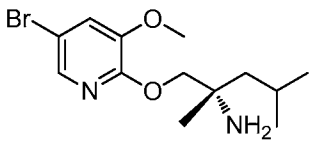
Obtained (*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloro-[3,4'-bipyridin]-2'-yl)carbamate(19.6 mg, 0.047 mmol, 85% yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.49 (d, *J*=2.2 Hz, 1H), 8.34 (d, *J*=5.1 Hz, 1H), 8.25 (d, *J*=2.2 Hz, 1H), 8.07 (s, 1H), 7.42 (dd, *J*=5.1, 1.5 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 $C_{19}H_{26}ClN_4O_3$, 393.2]; LC/MS retention time (method A): t_R = 1.98 min.

Example 56

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

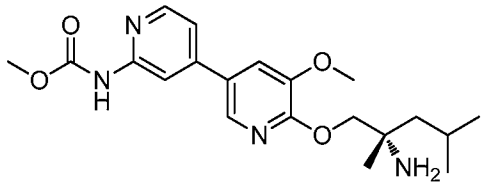


Prepared as in Example 51.



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.

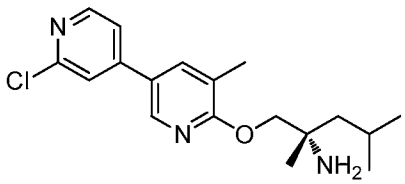


Part B: (S)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-methoxy-[3,4'-bipyridin]-2'-yl)carbamate.

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. ^{1}H 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 $C_{20}H_{29}N_4O4$, 389.2]; LC/MS retention time (method B): t_R = 1.64 min.

Example 57

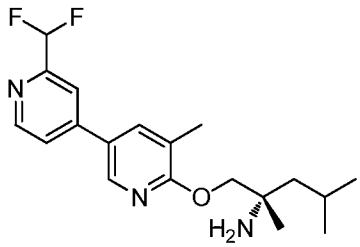
(*S*)-1-((2'-chloro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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]; LC/MS retention time (method B): t_R = 1.94 min.

Example 58

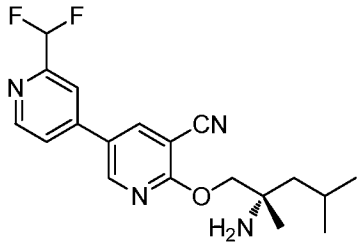
(*S*)-1-((2'-(difluoromethyl)-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



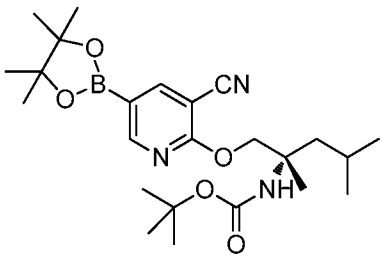
Prepared as in Example 51. Obtained (*S*)-1-((2'-(difluoromethyl)-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (15.1 mg, 0.043 mmol, 81% yield) as an off-white solid.. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, *J* = 5.2 Hz, 1H), 8.53 (d, *J* = 2.5 Hz, 1H), 8.12 (d, *J* = 2.5 Hz, 1H), 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* = 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 $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method A): t_R = 1.80 min.

Example 59

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

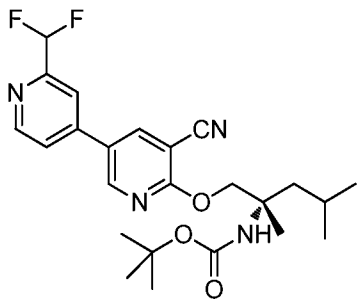


Prepared as in Example 51.



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

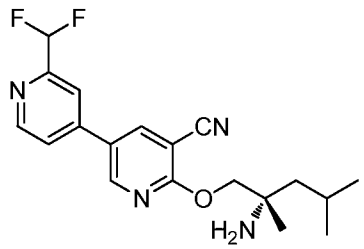
To a 20 mL vial was added (*S*)-*tert*-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (73 mg, 0.177 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (54.0 mg, 0.212 mmol), and potassium acetate (52.1 mg, 0.531 mmol) in dioxane (2 mL) with nitrogen bubbling to give a colorless suspension. $PdCl_2(dppf)$ (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 Na_2CO_3 (0.176 mL, 0.352 mmol) in dioxane (1 mL) (degassed with N_2) 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 (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was directly carried onto next reaction. LCMS (ESI) *m/e* 483.2 $[(M+Na)^+$, calcd $C_{24}H_{30}F_2N_4Na_1O_3$, 483.2]; LC/MS retention time (method B): t_R = 2.30 min.

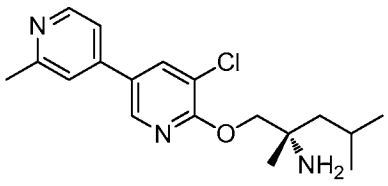


Part C: (S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-(difluoromethyl)-[3,4'-bipyridine]-5-carbonitrile.

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. ^{1}H NMR (500 MHz, DMSO-d_6) 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -73.65; LCMS (ESI) *m/e* 383.3 $[(M+Na)^+$, calcd $C_{19}H_{22}F_2N_4Na_1O_1$, 383.2]; LC/MS retention time (method B): t_R = 1.77 min.

Example 60

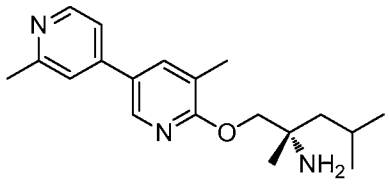
(*S*)-1-((5-chloro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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 umol, 31% yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{18}H_{25}ClN_3O$, 334.2]; LC/MS retention time (method A): t_R = 1.90 min.

Example 61

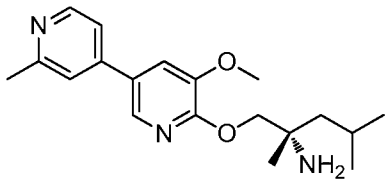
(*S*)-1-((2',5-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as in Example 51. Obtained (*S*)-1-((5-chloro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (20.5 mg, 0.065 mmol, 41% yield) as an off-white solid. ^{1}H 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 [(M-NH$_2$)$^+$, calcd $C_{19}H_{25}ClN_2O$, 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

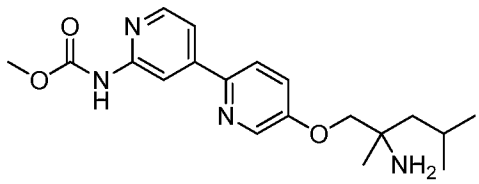


Prepared as in Example 51. Obtained (*S*)-1-((5-methoxy-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (20.5 mg, 0.065 mmol, 41% yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.48 (d, *J*=5.1 Hz, 1H), 8.14 (s, 1H), 7.65 (d, *J*=4.0 Hz, 2H), 7.55 (d, *J*=3.7 Hz, 1H), 4.06 (q, *J*=10.1 Hz, 2H), 3.93

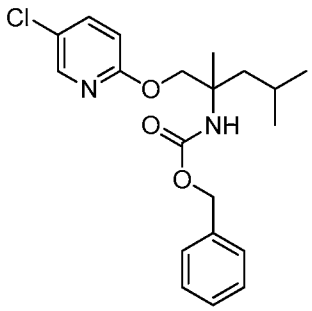
(s, 3H), 2.53 (s, 3H), 1.85 - 1.70 (m, 1H), 1.42 - 1.31 (m, 2H), 1.11 (s, 3H), 0.92 (t, *J*=7.0 Hz, 6H); LCMS (ESI) *m/e* 330.1 [(M+H)$^+$, calcd $C_{19}H_{28}N_3O_2$, 330.2]; LC/MS retention time (method B): t_R = 1.42 min.

Example 63

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

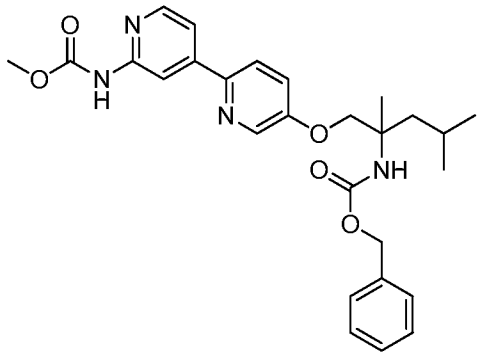


Prepared as in Example 29.



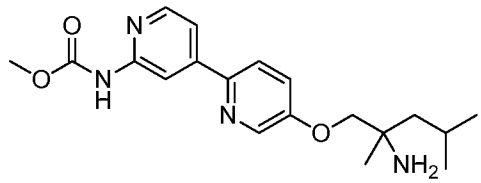
Part A: Benzyl (1-((5-chloropyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

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

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.

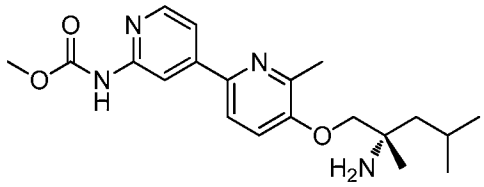


Part C: methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate

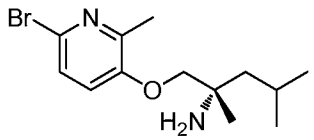
A mixture of Pd/C (4 mg, 3.76 μmol) and Cbz protected methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate (0.0123 g, 0.025 mmol) in ethanol (4 mL) was stirred under H_2 balloon at room temperature overnight. The reaction mixture was filtered and the flask was rinsed with CH_2Cl_2. The filter cake was washed with CH_2Cl_2. 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. ^{1}H NMR (600MHz, DMSO-d_6) 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 $C_{19}H_{27}N_4O3$, 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

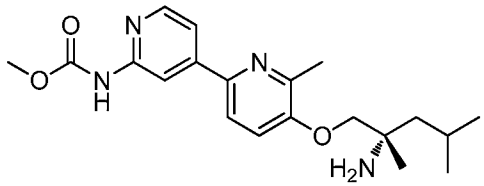


Prepared as in Example 19.



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

LCMS (ESI) *m/e* 284.2 $[(M-NH_2)^+$, calcd $C_{13}H_{19}BrNO$, 284.1]; LC/MS retention time (method A): t_R = 1.78 min (SM: t_R = 1.61 min).

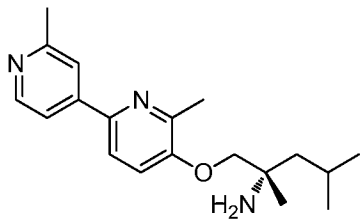


Part B: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate.

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. . ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{20}H_{29}N_4O_3$, 373.2]; LC/MS retention time (method A): t_R = 1.82 min.

Example 65

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

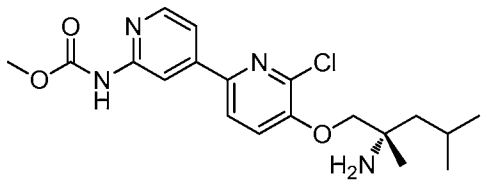


Prepared as in Example 51. Obtained ((*S*)-1-((2',6-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (7.2 mg, 0.022 mmol, 29% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, *J* = 5.3 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 5.3 Hz, 1H), 7.43 (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,

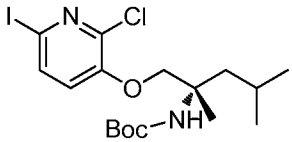
2H), 1.15 (s, 3H), 0.94 (t, J = 6.2 Hz, 6H); LCMS (ESI) m/e 314.4 [$(M+H)^+$, calcd $C_{19}H_{28}N_3O$, 314.2]; LC/MS retention time (method A): t_R = 1.84 min.

Example 66

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

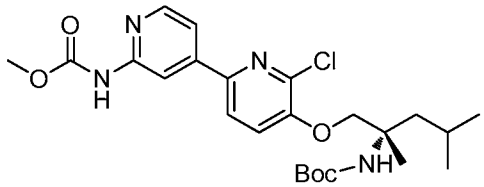


Prepared as in Example 32.



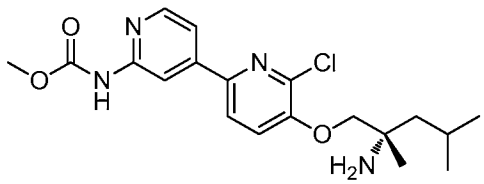
Part A: (S)-tert-butyl (1-((2-chloro-6-iodopyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

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.

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.

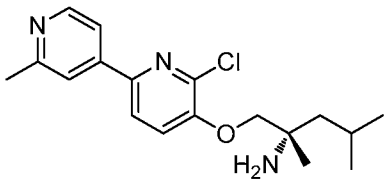


Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate.

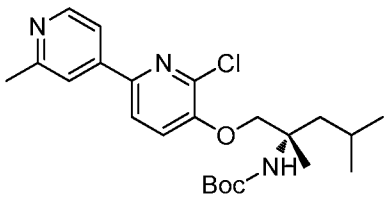
Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-chloro-[2,4'-bipyridin]-2'-yl)carbamate (12.6 mg, 0.032 mmol, 69% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.35 (d, *J* = 5.3 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 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 $C_{19}H_{26}Cl_1N_4O_3$, 393.2]; LC/MS retention time (method A): t_R = 1.66 min.

Example 67

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

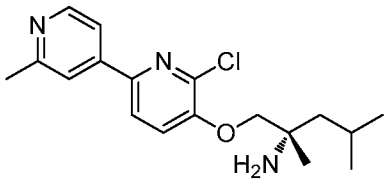


Prepared as in Example 32.



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

Synthesis followed previous procedure. LCMS (ESI) *m/e* 434.0 [(M+H)$^+$, calcd $C_{23}H_{33}Cl_1N_3O_3$, 434.2]; LC/MS retention time (method B): t_R = 1.96 min.

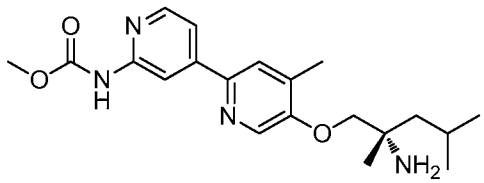


Part B: (S)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine.

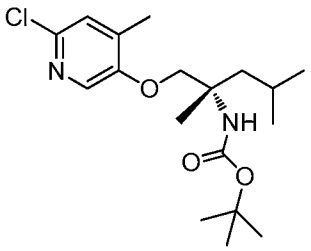
Obtained (*S*)-1-((6-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (4.6 mg, 0.013 mmol, 30% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, *J* = 5.2 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.85 (s, 1H), 7.76 (d, *J* = 5.3 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 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 $C_{18}H_{25}Cl_1N_3O_1$, 334.2]; LC/MS retention time (method A): t_R = 1.48 min.

Example 68

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

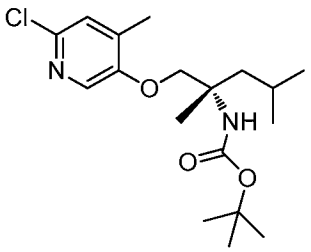


Prepared as in Example 32.



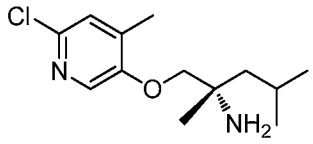
Part A: (S)-tert-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) *m/e* 357.3 [(M+H)$^+$, calcd $C_{18}H_{30}ClN_2O_3$, 357.2]; LC/MS retention time (method A): t_R = 2.23 min.



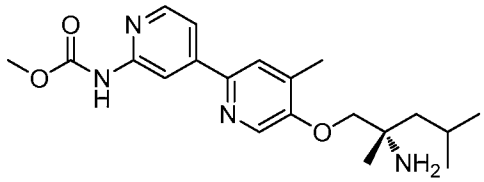
Part B: (S)-tert-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

LCMS (ESI) *m/e* 357.3 [(M+H)$^+$, calcd $C_{18}H_{30}ClN_2O_3$, 357.2]; LC/MS 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 retention time (method B): t_R = 1.70 min.

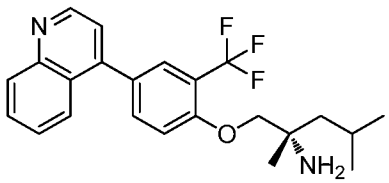


Part D: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate.

Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methyl-[2,4'-bipyridin]-2'-yl)carbamate (1.1 mg, 2.92 umol, 5% yield) as an off-white solid. ^{1}H 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 (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

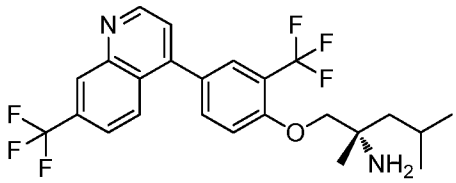


Prepared as in Example 32. Obtained (*S*)-2,4-dimethyl-1-(4-(quinolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (50 mg, 0.123 mmol, 17%yield) as a brown solid.^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.96 (d, *J*=4.5 Hz, 1H), 8.20

(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, *J*=5.5 Hz, 2H), 1.28 (s, 3H), 1.06 - 0.98 (m, 6H); ^{19}F NMR (376MHz, CHLOROFORM-d) δ -62.29 (s, 3F); LCMS (ESI) *m/e* 403.2 [$(M+H)^+$, calcd $C_{23}H_{26}F_3N_2O$, 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

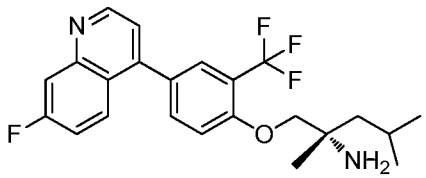


Prepared as in Example 32. A mixture of 2-(dicyclohexylphosphino)-2',4',6'-triisopropylbiphenyl (2.90 mg, 6.09 µmol), potassium acetate (0.090 g, 0.913 mmol), 2nd generation Xphos precatalyst (2.395 mg, 3.04 µmol), 4-chloro-8-(trifluoromethyl)quinoline (0.0705 g, 0.304 mmol) and hypodiboric acid (0.041 g, 0.457 mmol) in ethanol (4 mL) was degassed three times via vacuum/N_2 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-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 (Na_2SO_4), 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. ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{24}H_{25}F_6N_2O$, 471.2]; LC/MS retention time (method A): t_R = 2.28 min.

Example 71

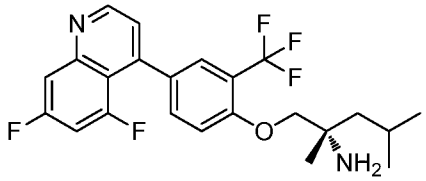
(*S*)-1-(4-(7-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (500MHz, DMSO-d_6) 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-NH_2)$^+$, calcd $C_{23}H_{22}F_4NO$, 404.2]; LC/MS retention time (method B): t_R = 1.88 min.

Example 72

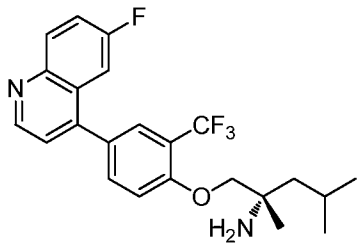
(S)-1-(4-(5,7-difluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{23}H_{24}F_5N_2O$, 439.2]; LC/MS retention time (method A): t_R = 2.14 min.

Example 73

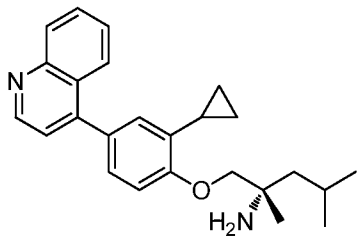
(*S*)-1-(4-(6-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine



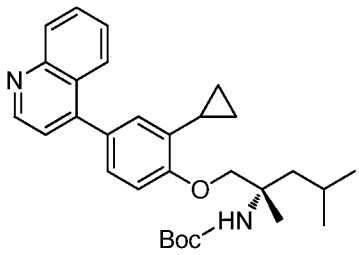
Prepared as in Example 32. Obtained (*S*)-1-(4-(6-fluoroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (9.6 mg, 0.023 mmol, 22%yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.95 (d, *J* = 4.4 Hz, 1H), 8.21 (dd, *J* = 9.2, 5.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -61.01 , -244.69; LCMS (ESI) *m/e* 421.2 [(M+H)$^+$, calcd $C_{23}H_{25}F_4N_2O_1$, 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

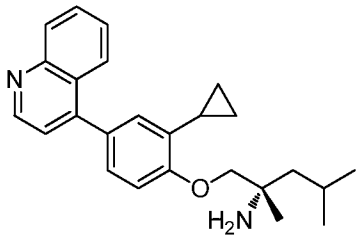


Prepared as in Example 32.



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

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.

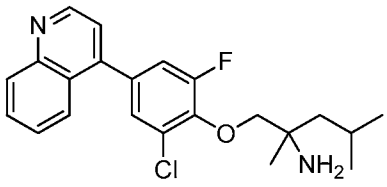


Part B: (S)-1-(2-cyclopropyl-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine.

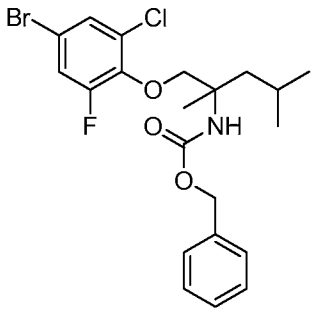
Obtained (12.7 mg, 0.032 mmol, 33%yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (d, J = 4.4 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.42 (d, J = 4.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 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 (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

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

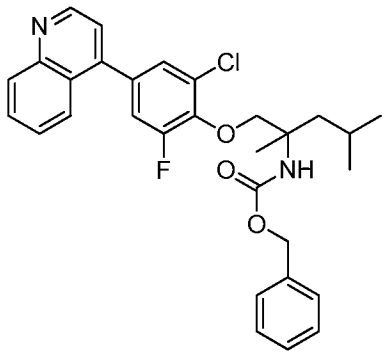


Prepared as in Example 29.



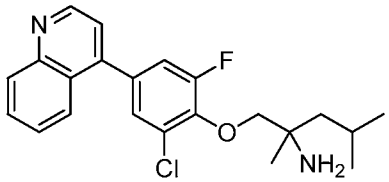
Part A: Benzyl (1-(4-bromo-2-chloro-6-fluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate.

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 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 $C_{21}H_{24}ClBrFNO_3Na$, 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 retention time (method A): t_R = 2.38 min.

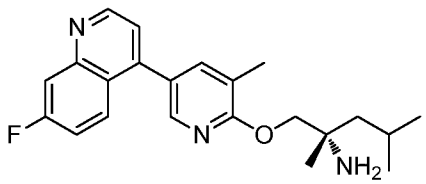


Part C: 1-(2-chloro-6-fluoro-4-(quinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

Triethylsilane(0.1 ml, 0.626 mmol) was added to a CH_2Cl_2 (0.2 mL) suspension of palladium(II) acetate(2 mg, 8.91 μmol) 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 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.) ^{1}H NMR (500MHz, DMSO-d6) 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 $C_{22}H_{25}FClN_2O$, 387.2]; LC/MS retention time (method B): t_R = 1.70 min.

Example 76

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

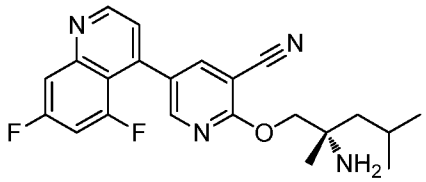


Intermediates prepared as described in Example 19. A mixture of potassium acetate (0.026 g, 0.266 mmol), (*S*)-1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0267 g, 0.089 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-

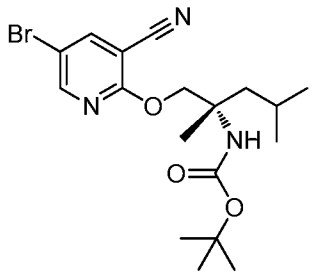
bi(1,3,2-dioxaborolane) (0.027 g, 0.106 mmol) in dioxane (1 mL) underwent vacuum/backfill N_2 (5X). $PdCl_2(dppf)$ (1.946 mg, 2.66 µmol) was added to the reaction mixture and the reaction was heated at 80 °C overnight. The reaction mixture was cooled to room temperature. $PdCl_2(dppf)$ (3.26 mg, 4.45 µmol), 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

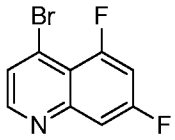


Prepared as in Example 53.



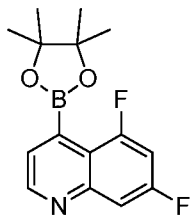
Part A: (S)-tert-butyl (1-((5-bromo-3-cyanopyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate.

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

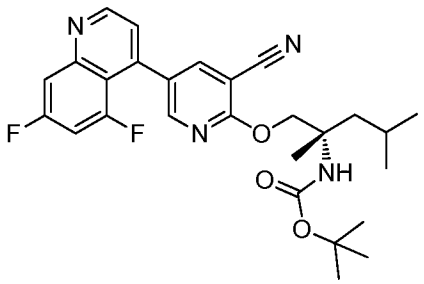
To a 20 mL microwave tube was added 4-chloro-5,7-difluoroquinoline (0.159 g, 0.795 mmol) and propionitrile (1mL), followed by TMS-Br (0.206 mL, 1.59 mmol) at room temperature. A precipitate formed. The tube was sealed and heated to 100°C overnight. The reaction was cooled to room temperature. The crude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



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

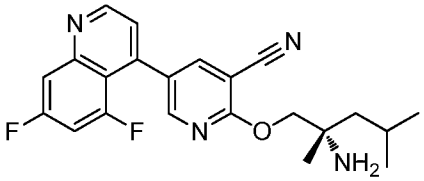
A mixture of potassium acetate (0.122 g, 1.242 mmol), 4-bromo-5,7-difluoroquinoline (0.1010 g, 0.414 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-

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 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.



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 µmol), 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 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.

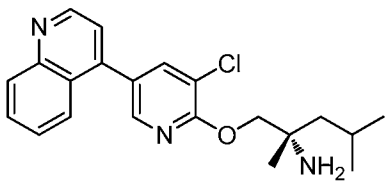


Part E: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5,7-difluoroquinolin-4-yl)nicotinonitrile.

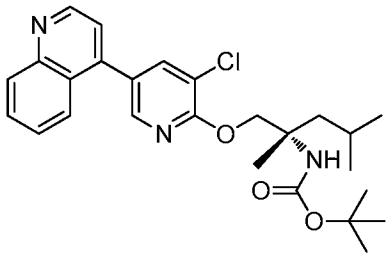
^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.04 (d, *J*=4.4 Hz, 1H), 8.59 (s, 1H), 8.54 (br. s., 1H), 7.82 (d, *J*=9.2 Hz, 1H), 7.70 - 7.59 (m, 1H), 7.54 (d, *J*=4.4 Hz, 1H), 4.30 - 4.17 (m, 2H), 3.44 (br. s., 2H), 1.87 - 1.79 (m, 1H), 1.50 - 1.36 (m, 2H), 1.16 (s, 3H), 0.96 (d, *J*=2.9 Hz, 3H), 0.94 (d, *J*=2.9 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.

Example 78

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

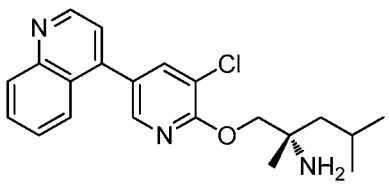


Prepared as in Example 77.



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.

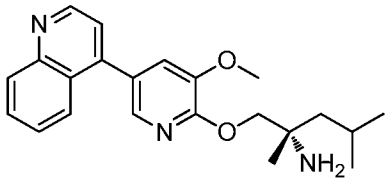


Part B: (S)-1-((3-chloro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine.

^{1}H 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.

Example 79

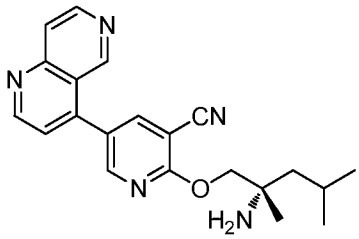
(*S*)-1-((3-methoxy-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



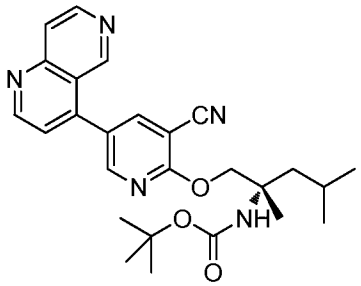
Prepared as in Example 77. Obtained (*S*)-1-((3-methoxy-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (5.4 mg, 0.014 mmol, 23%yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.96 (d, *J*=4.4 Hz, 1H), 8.12 (d, *J*=8.4 Hz, 1H), 7.97 (d, *J*=8.4 Hz, 1H), 7.86 (d, *J*=1.5 Hz, 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.

Example 80

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

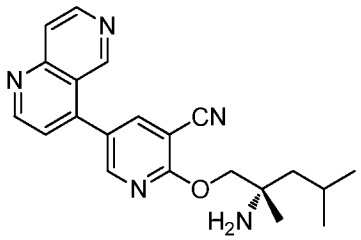


Prepared as in Example 77.



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

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.

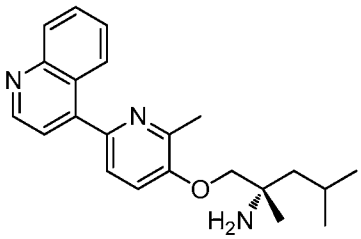


Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)nicotinonitrile.

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. ^{1}H 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* = 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.

Example 81

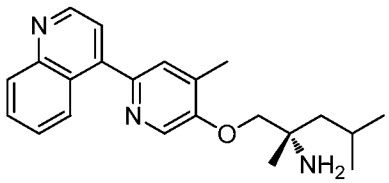
(*S*)-2,4-dimethyl-1-((2-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine



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. ^{1}H 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.

Example 82

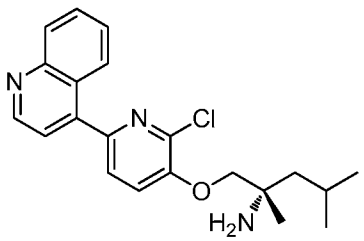
(*S*)-2,4-dimethyl-1-((4-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine



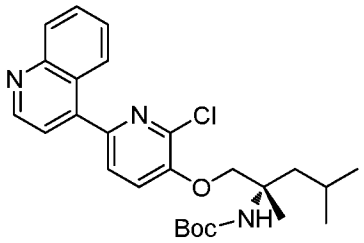
Prepared as in Example 77. Obtained (*S*)-2,4-dimethyl-1-((4-methyl-6-(quinolin-4-yl)pyridin-3-yl)oxy)pentan-2-amine (11 mg, 0.030 mmol, 39%yield) as an off-white solid. ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.97 (d, *J*=4.4 Hz, 1H), 8.44 (s, 1H), 8.25 (d, *J*=8.8 Hz, 1H), 8.10 (d, *J*=8.4 Hz, 1H), 7.80 (t, *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.

Example 83

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

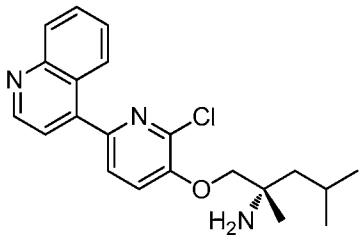


Prepared as in Example 77.



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 $C_{26}H_{33}Cl_1N_3O_3$, 470.2]; LC/MS retention time (method B): t_R = 2.15 min.

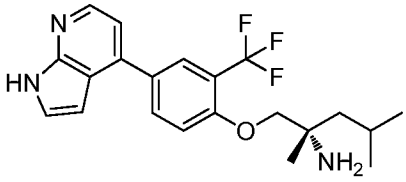


Part B: (S)-1-((2-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Obtained (6.3 mg, 0.016 mmol, 36%yield) as an off-white solid. . ^{1}H 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 $C_{21}H_{25}Cl_1N_3O_1$, 370.2]; LC/MS retention time (method B): t_R = 1.57 min.

Example 84

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

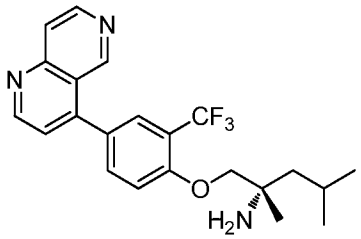


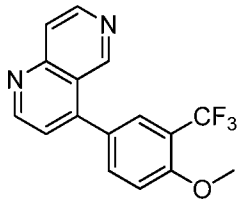
Prepared as in Example 19 to obtain (*S*)-1-(4-(1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (27 mg, 0.069 mmol, 79%

yield) as an off-white solid. ^{1}H 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); ^{19}F NMR (376MHz, CHLOROFORM-d) δ -62.31 (s, 3F); LCMS (ESI) *m/e* 392.2 [$(M+H)^+$, calcd $C_{21}H_{25}F_3N_3O$, 392.2]; LC/MS retention time (method B): t_R = 1.81 min.

Example 85

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

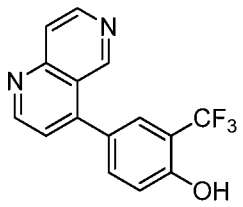




Part A: 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine.

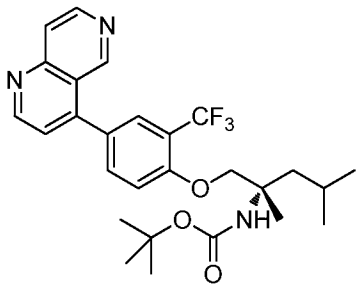
To a 20 mL vial was added 4-chloro-1,6-naphthyridine (200 mg, 1.215 mmol), (4-methoxy-3-(trifluoromethyl)phenyl)boronic acid (321 mg, 1.458 mmol), and potassium phosphate tribasic (4.86 mL, 2.430 mmol) in THF (2.5 mL) to give a yellow suspension. After degassing with N_2 for 5 min, 2nd generation XPHOS 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 (Na_2SO_4) and concentrated under reduced pressure . The residue was purified by silica gel chromatography (up to 8% MeOH/CH_2Cl_2) to afford 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine (369 mg, 1.213 mmol, quantitative yield) as a light yellow solid: ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -62.63; LCMS (ESI) *m/e* 305.2 [$(M+H)^+$, calcd $C_{16}H_{12}F_3N_2O_1$, 305.1]; LC/MS retention time (method A): t_R = 1.86 min.



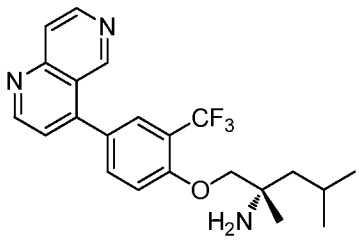
Part B: 4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenol

To a 250 mL round-bottomed flask was added 4-(4-methoxy-3-(trifluoromethyl)phenyl)-1,6-naphthyridine (369 mg, 1.213 mmol) in CH_2Cl_2 (5 mL) under nitrogen to give a yellow solution. BBr_3 (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 (Na_2SO_4) and concentrated under reduced pressure . The residue was purified by silica gel chromatography (up to 8% MeOH/CH_2Cl_2) to afford 4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenol (124 mg, 0.427 mmol, 35%) as a white solid: ^{1}H 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); ^{19}F 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.



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.

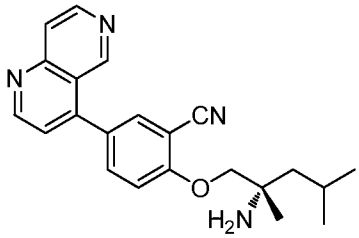


Part D: (S)-1-(4-(1,6-naphthyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine.

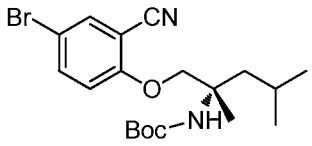
Obtained (35.7 mg, 0.087 mmol, 99% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d6) δ 9.26 (s, 1H), 9.17 (d, *J* = 4.5 Hz, 1H), 8.80 (d, *J* = 5.8 Hz, 1H), 8.01 (d, *J* = 5.9 Hz, 1H), 7.95 (d, *J* = 8.7 Hz, 1H), 7.90 (s, 1H), 7.69 (d, *J* = 4.4 Hz, 1H), 7.47 (d, *J* = 8.6 Hz, 1H), 3.94 (q, *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); 19F 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.

Example 86

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

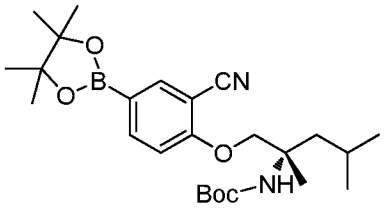


Prepared as in Example 51.



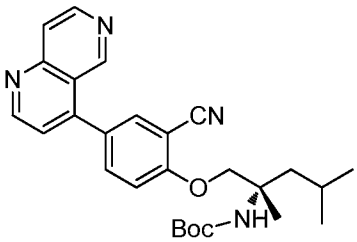
Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate.

^{1}H 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 $C_{19}H_{27}Br_1N_2Na_1O_3$, 433.1]; LC/MS retention time (method B): t_R = 2.38 min.



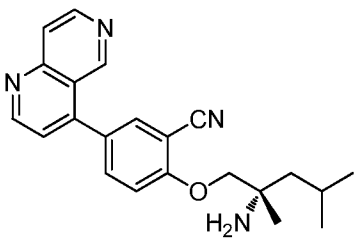
Part B: (S)-tert-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

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 $C_{27}H_{32}N_4Na_1O_3$, 483.2]; LC/MS retention time (method B): t_R = 2.10 min.

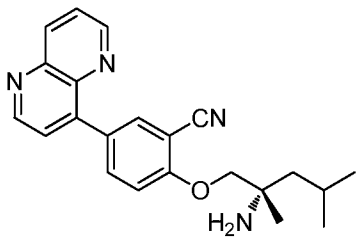


Part D: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile.

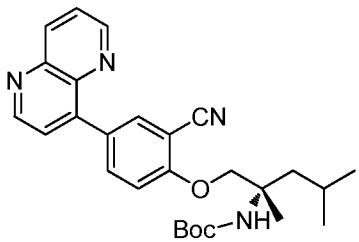
Obtained (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,6-naphthyridin-4-yl)benzonitrile (6.7 mg, 0.017 mmol, 34% yield) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.27 (s, 1H), 9.17 (d, *J* = 4.5 Hz, 1H), 8.80 (d, *J* = 5.8 Hz, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 8.01 (d, *J* = 5.8 Hz, 1H), 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* = 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 $C_{22}H_{25}N_4O_1$, 361.2]; LC/MS retention time (method B): t_R = 1.58 min.

Example 87

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

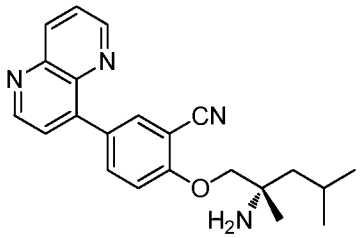


Prepared as in Example 51.



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 $C_{27}H_{32}N_4Na_1O_3$, 483.2]; LC/MS retention time (method B): t_R = 2.22 min.

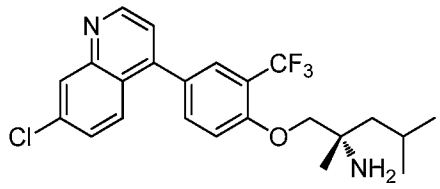


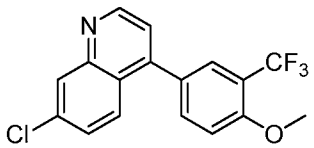
Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(1,5-naphthyridin-4-yl)benzonitrile.

Obtained (5.5 mg, 0.015 mmol, 29% yield) as an off-white solid. ^{1}H 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 $C_{22}H_{25}N_4O_1$, 361.2]; LC/MS retention time (method B): t_R = 1.68 min.

Example 88

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

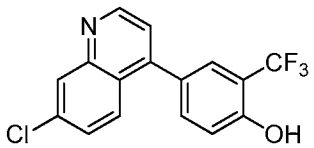




Part A: 7-chloro-4-(4-methoxy-3-(trifluoromethyl)phenyl)quinoline

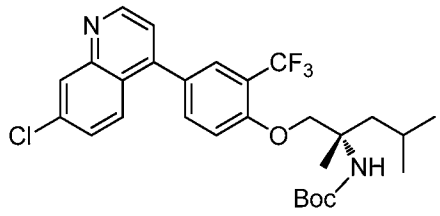
A mixture of 4,7-dichloroquinoline (810 mg, 4.09 mmol), (4-methoxy-3-(trifluoromethyl)phenyl)boronic acid (900 mg, 4.09 mmol), $PdCl_2$(dppf) (150 mg, 0.205 mmol), cesium carbonate (2000 mg, 6.14 mmol), and 1,4-dioxane (10 mL) were charged to a 20 mL pressure rated vial and a stream of nitrogen was bubbled 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 reside was purified by silica gel chromatography (5-40 % ethyl acetate/hexanes gradient elution) to afford7-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 $C_{17}H_{12}ClF_3NO$, 338.1]; LC/MS retention time (method D): t_R = 1.13 min.



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

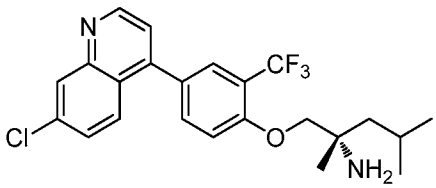
A solution of 7-chloro-4-(4-methoxy-3-(trifluoromethyl)phenyl)quinoline (0.51 g, 1.510 mmol) in dichloromethane (10 mL) 0 °C was treated with BBr_3 (3.02 mL, 3.02 mmol). The cooling bath was removed and the reaction solution stirred at ambient temperature overnight. The resultant was cooled to 0 °C and quenched with 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 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.



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

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 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; ^{1}H 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).



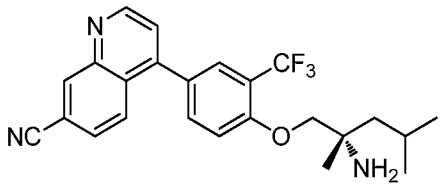
Part D: (S)-1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

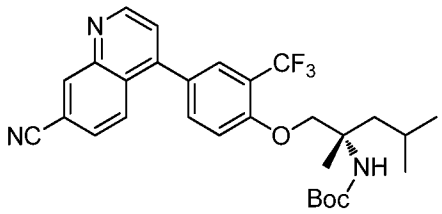
(*S*)-*tert*-Butyl (1-(4-(7-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (40 mg, 0.074 mmol) was treated with TFA (1 mL, 12.98 mmol) and stirred at ambient temperature for 30 min. The resultant was concentrated under reduced pressure. The residue was purified via preparative LC/MS (Column: XBridge C18, 19 x 200 mm, 5-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*)-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 $C_{23}H_{25}ClF_3N_2O$, 437.2]; LC/MS retention time (method D): t_R = 0.97 min; ^{1}H 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

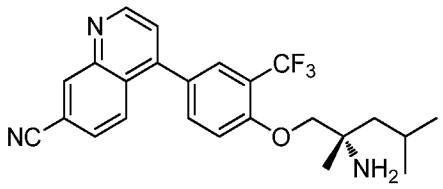




Part A: (*S*)-*tert*-butyl (1-(4-(7-cyanoquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

(*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 $C_{29}H_{33}F_3N_3O_3$, 528.3]; LC/MS retention time (method D): t_R = 1.30 min.

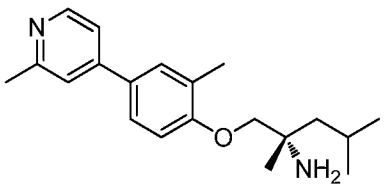


Part B: (S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)quinoline-7-carbonitrile

(*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 (13.3 mg, 0.031 mmol, 75% yield) as a colorless solid. LCMS (ESI) *m/e* 428.2 [$(M+H)^+$, calcd $C_{24}H_{25}F_3N_3O$, 428.2]; LC/MS retention time (method D): t_R = 0.97 min; ^{1}H NMR (500MHz, DMSO-d_6) 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, 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

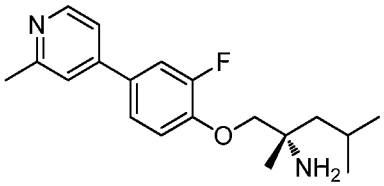
(*S*)-2,4-dimethyl-1-(2-methyl-4-(2-methylpyridin-4-yl)phenoxy)pentan-2-amine



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 $C_{20}H_{29}N_2O$, 313.2]; LC/MS retention time (method D): t_R = 0.65 min; ^{1}H NMR (500MHz, DMSO-d_6) 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).

Example 91

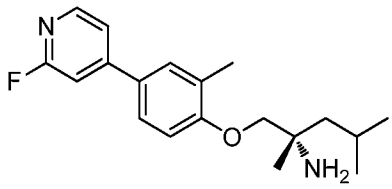
(*S*)-1-(2-fluoro-4-(2-methylpyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



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 $C_{19}H_{26}FN_2O$, 317.2]; LC/MS retention time (method D): t_R = 0.62 min; ^{1}H NMR (500MHz, DMSO-d_6) 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).

Example 92

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

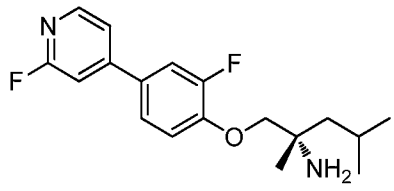


Prepared as described in Example 32 to afford (*S*)-1-(4-(2-fluoropyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine (4.8 mg, 0.015 mmol, 90% yield

for the final step) as a colorless solid. LCMS (ESI) *m/e* 317.1 [$(M+H)^+$, calcd $C_{19}H_{26}FN_2O$, 317.2]; LC/MS retention time (method D): t_R = 0.96 min; ^1H NMR (500MHz, DMSO-d_6) 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).

Example 93

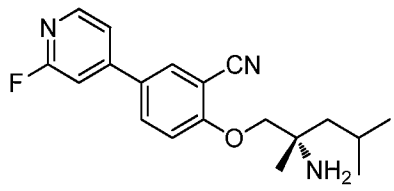
(*S*)-1-(2-fluoro-4-(2-fluoropyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



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 $C_{18}H_{23}F_2N_2O$, 321.2]; LC/MS retention time (method D): t_R = 0.90 min; ^1H NMR (500MHz, DMSO-d_6) 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

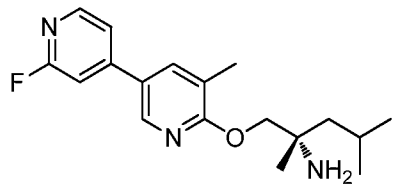


Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-fluoropyridin-4-yl)benzonitrile (16.9 mg, 0.051 mmol, 80% yield for the final step) as a colorless solid. LCMS (ESI) *m/e* 328.1 [$(M+H)^+$, calcd $C_{19}H_{23}FN_3O$, 328.2]; LC/MS retention time (method D): t_R = 0.94 min; ^1H NMR (500MHz, DMSO-d_6) 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

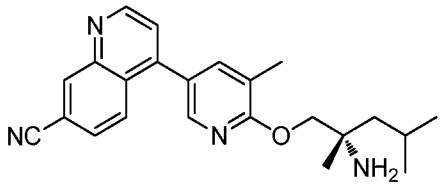
(*S*)-1-((2'-fluoro-5-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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 $C_{18}H_{25}FN_3O$, 318.2]; LC/MS retention time (method D): t_R = 0.95 min; ^{1}H NMR (500MHz, DMSO-d_6) 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

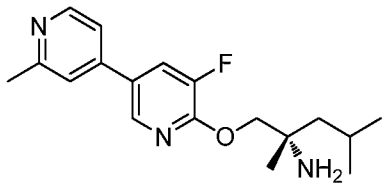
(*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)quinoline-7-carbonitrile



Prepared as described in Example 88 to afford (*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)quinoline-7-carbonitrile (9.9 mg, 0.026 mmol, 35% yield for the final step) as a colorless solid. LCMS (ESI) *m/e* 375.1 [$(M+H)^+$, calcd $C_{23}H_{27}N_4O$, 375.2]; LC/MS retention time (method D): t_R = 0.94 min; ^{1}H NMR (600MHz, DMSO-d_6) 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), 1.16 (s, 3H), 0.95 (t, *J*=6.2 Hz, 6H).

Example 97

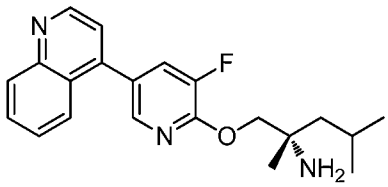
(*S*)-1-((5-fluoro-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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 $C_{18}H_{25}FN_3O$, 318.2]; LC/MS retention time (method D): t_R = 0.60 min; ^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, *J*=5.1 Hz, 1H), 8.48 (s, 1H), 8.23 (d, *J*=11.4 Hz, 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

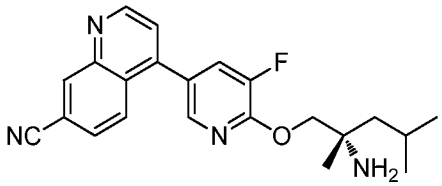
(*S*)-1-((3-fluoro-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



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 $C_{21}H_{25}FN_3O$, 354.2]; LC/MS retention time (method D): t_R = 0.74 min; ^{1}H 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

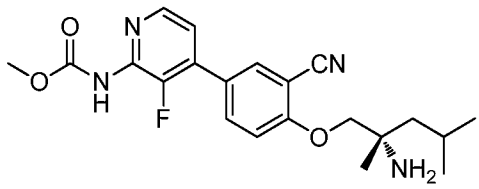
(*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)quinoline-7-carbonitrile

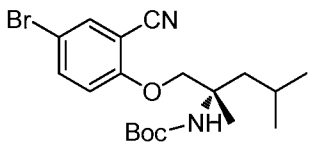


Prepared as described in Example 88 to (*S*)-4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)quinoline-7-carbonitrile (5.6 mg, 0.014 mmol, 62% yield for the final step) as a colorless solid. LCMS (ESI) *m/e* 379.1 $[(M+H)^+$, calcd $C_{22}H_{24}FN_4O$, 379.2]; LC/MS retention time (method D): t_R = 0.91 min; ^{1}H 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

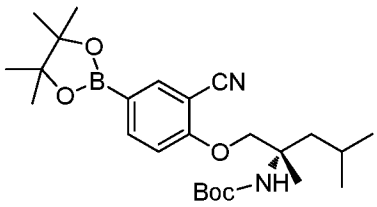
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate





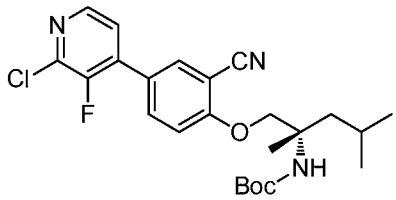
Part A: (S)-tert-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate

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.



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

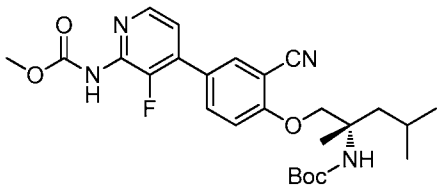
(*S*)-*tert*-butyl (1-(4-bromo-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.57 g, 1.386 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.422 g, 1.663 mmol), $PdCl_2$(dppf) (0.051 g, 0.069 mmol), potassium acetate (0.408 g, 4.16 mmol), and dioxane (5 mL) were charged to a 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 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.



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

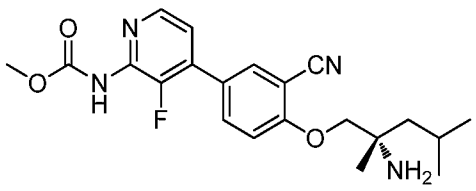
A mixture of 2-chloro-3-fluoro-4-iodopyridine (105 mg, 0.408 mmol), (*S*)-*tert*-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (374 mg, 0.816 mmol), potassium carbonate (169 mg, 1.224 mmol), and $Pd(Ph_3P)_4$ (14.14 mg, 0.012 mmol) in toluene (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

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), 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 $C_{23}H_{30}ClFN_3O_3$, 501.3]; LC/MS retention time (method D): t_R = 1.17 min.

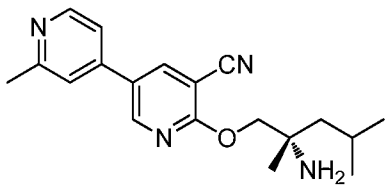


Part E: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-3-fluoropyridin-2-yl)carbamate

(*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 □mol, 25% yield for two steps) as a colorless solid. LCMS (ESI) *m/e* 401.0 $(M+H)^+$, calcd $C_{21}H_{26}FN_4O_3$, 401.2]; LC/MS retention time (method D): t_R = 0.82 min; ^{1}H NMR (500MHz, DMSO-d_6) 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

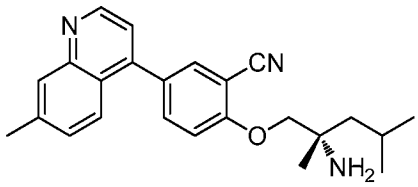
(*S*)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methyl-[3,4'-bipyridine]-5-carbonitrile



Prepared as described in Example 32 to afford (*S*)-6-((2-amino-2,4-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 $C_{19}H_{25}N_4O$, 325.2]; LC/MS retention time (method D): t_R = 0.58 min; ^{1}H NMR (500MHz, DMSO-d_6) 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, 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

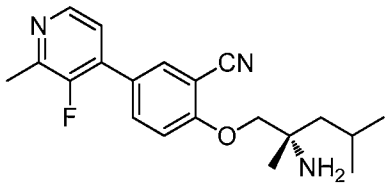
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(7-methylquinolin-4-yl)benzonitrile



Prepared as described in Example 32 to afford (*S*)-2-((2-amino-2,4-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 $C_{24}H_{28}N_3O$, 374.2]; LC/MS retention time (method D): t_R = 0.76 min; ^{1}H NMR (600MHz, DMSO-d_6) 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 (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).

Example 103

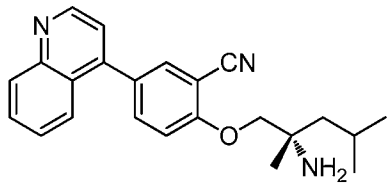
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(3-fluoro-2-methylpyridin-4-yl)benzonitrile



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 $C_{20}H_{25}FN_3O$, 342.2]; LC/MS retention time (method D): t_R = 0.79 min; ^{1}H NMR (600MHz, DMSO-d_6) 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

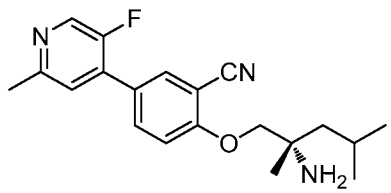
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(quinolin-4-yl)benzonitrile



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 $C_{23}H_{26}N_3O$, 360.2]; LC/MS retention time (method D): t_R = 0.69 min; ^{1}H NMR (600MHz, DMSO-d_6) 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

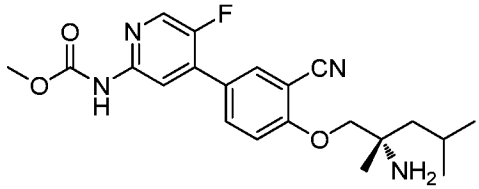
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(5-fluoro-2-methylpyridin-4-yl)benzonitrile



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 $C_{20}H_{25}FN_3O$, 342.2]; LC/MS retention time (method D): t_R = 0.80 min; ^{1}H NMR (500MHz, DMSO-d_6) 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), 0.94 (d, *J*=3.7 Hz, 3H), 0.93 (d, *J*=3.7 Hz, 3H).

xample 106

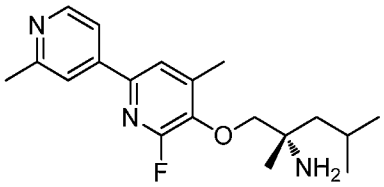
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-5-fluoropyridin-2-yl)carbamate

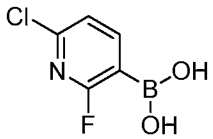


Prepared as described in Example 100 to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)-5-fluoropyridin-2-yl)carbamate (20.5 mg, 0.050 mmol, 36% yield for the final step) as a colorless film. LCMS (ESI) *m/e* 401.0 $(M+H)^+$, calcd $C_{21}H_{26}FN_4O_3$, 401.2]; LC/MS retention time (method D): t_R = 0.91 min; ^{1}H NMR (500MHz, DMSO-d_6) 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).

Example 107

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

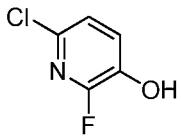




Part A: (6-chloro-2-fluoropyridin-3-yl)boronic acid

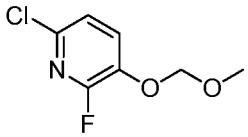
A solution of LDA (1M in THF) (8.36 ml, 8.36 mmol) at -78 °C was treated dropwise with a solution of 2-chloro-6-fluoropyridine (1.0 g, 7.60 mmol) in THF (2 mL). The mixture was maintained at -78 °C for 1 h and then treated with a solution of triisopropyl borate (1.765 ml, 7.60 mmol) in THF (1 mL). The 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 $C_5H_5BClFNO_2$, 176.0]; LC/MS retention time (method D): t_R = 0.71 min.



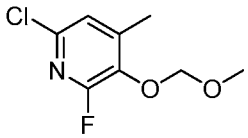
Part B: 6-chloro-2-fluoropyridin-3-ol

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* 148.0 $(M+H)^+$, calcd C_5H_4ClFNO, 148.0]; LC/MS retention time (method D): t_R = 0.83 min.



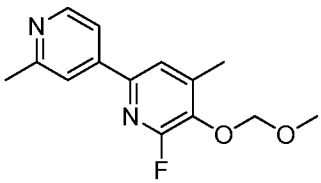
Part C: 6-chloro-2-fluoro-3-(methoxymethoxy)pyridine

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 $C_7H_8ClFNO_2$, 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

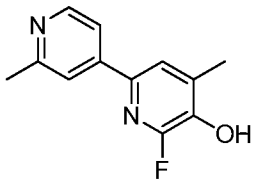
A solution of 6-chloro-2-fluoro-3-(methoxymethoxy)pyridine (0.24 g, 1.253 mmol) in tetrahydrofuran (9 mL) at -78 °C was treated dropwise with LDA (1.378 mL, 1.378 mmol). The resulting orange solution was maintained at -78 °C for 1 h and then treated dropwise with a solution of methyl iodide (0.094 mL, 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 $C_8H_{10}ClFNO_2$, 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).



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

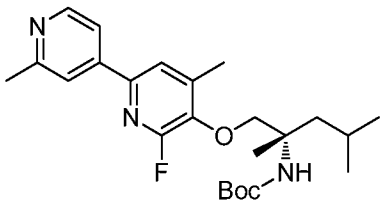
To a pressure rated vial was added 6-chloro-2-fluoro-3-(methoxymethoxy)-4-methylpyridine (110 mg, 0.535 mmol), (2-methylpyridin-4-yl)boronic acid (81 mg, 0.588 mmol), cesium carbonate (349 mg, 1.070 mmol), toluene (1 mL), and ethanol (0.200 mL). The solution was sparged with a stream of nitrogen for 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 $C_{14}H_{16}FN_2O_2$, 263.1]; LC/MS retention time (method D): t_R = 0.80 min; ^{1}H 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).



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

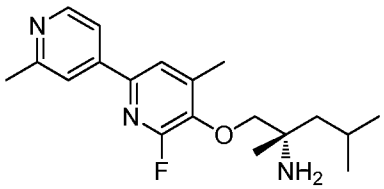
A solution of 6-fluoro-5-(methoxymethoxy)-2',4-dimethyl-2,4'-bipyridine (40 mg, 0.153 mmol) in methanol (5 mL) and HCl (conc.) (0.05 mL, 0.600 mmol) was stirred at 65 °C for 1 h and then concentrated under reduced pressure to afford 6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-ol (30 mg, 0.137 mmol, 90 % yield) as a pale tan solid. Used without further purification. LCMS (ESI) *m/e* 219.1 $(M+H)^+$, calcd $C_{12}H_{12}FN_2O$, 219.1]; LC/MS retention time (method D): t_R = 0.59 min.



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 $C_{24}H_{35}FN_3O_3$, 432.3]; LC/MS retention time (method D): t_R = 1.08 min.

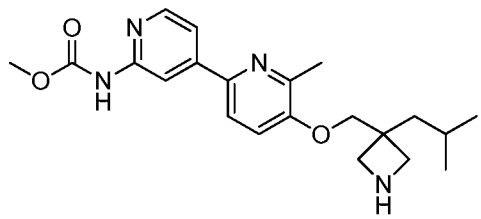


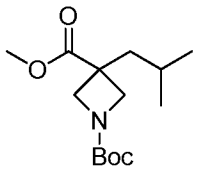
Part H: (*S*)-1-((6-fluoro-2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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 $C_{19}H_{27}FN_3O$, 332.2]; LC/MS retention time (method D): t_R = 0.64 min; ^{1}H 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

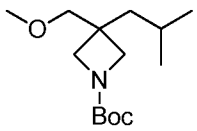
methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate





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

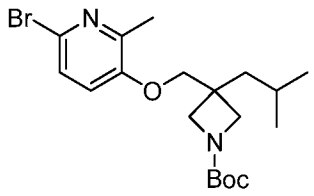
A solution of 1-*tert*-butyl 3-methyl azetidine-1,3-dicarboxylate (5.0 g, 23.23 mmol) and 1-iodo-2-methylpropane (21.37 g, 116 mmol) in tetrahydrofuran (100 mL) at -78 °C was treated dropwise with KHMDS (69.7 mL, 34.8 mmol). The solution was stirred at ambient temperature overnight. The resulting suspension 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. ^{1}H 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).



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

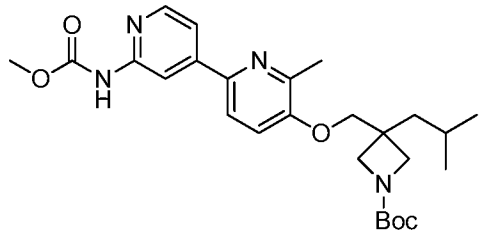
A solution of 1-*tert*-butyl 3-methyl 3-isobutylazetidine-1,3-dicarboxylate (2.51 g, 9.25 mmol) in tetrahydrofuran (40 mL) at ambient temperature was treated with lithium borohydride (0.403 g, 18.50 mmol) and stirred at 70 °C for 3 h. TLC indicated 50 % consumption of starting material. The reaction mixture was treated 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 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. ^{1}H 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), 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

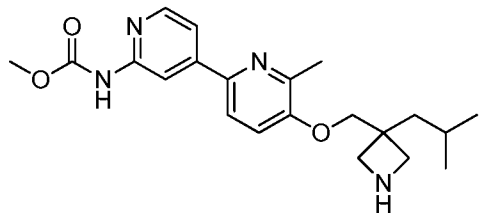
A solution of *tert*-butyl 3-(hydroxymethyl)-3-isobutylazetidine-1-carboxylate (0.582 g, 2.392 mmol) in tetrahydrofuran (4 mL) was charged to a pressure rated vial and treated dropwise with KOtBu (1M in THF) (2.392 mL, 2.392 mmol). After 5 minutes, 6-bromo-3-fluoro-2-methylpyridine (0.50 g, 2.63 mmol) 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 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 $(M\text{-}Boc+H)^+$, calcd $C_{14}H_{22}BrN_2O$, 313.1]; LC/MS retention time (method D): t_R = 0.92 min.



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), $Pd(Ph_3P)_4$ (13.76 mg, 0.012

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 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 $C_{26}H_{37}N_4O_5$, 485.3]; LC/MS retention time (method D): t_R = 1.14 min.

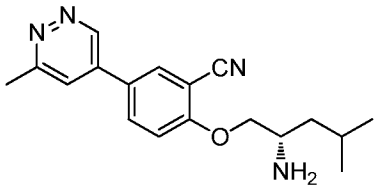


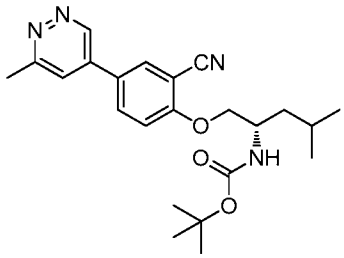
Part D: methyl (5-((3-isobutylazetidin-3-yl)methoxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

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-µm; 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 $C_{21}H_{29}N_4O_3$, 385.3]; LC/MS retention time (method D): t_R = 0.76 min; ^1H NMR (500MHz, DMSO-d_6) 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

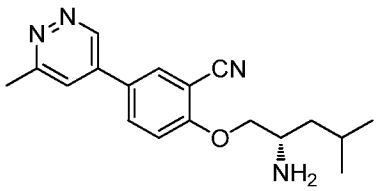
(*S*)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile





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 Na_2CO_3 (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 Na_2SO_4, and passed through a plug of Na_2SO_4. 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 $C_{23}H_{31}N_4O_3$, 411.2].



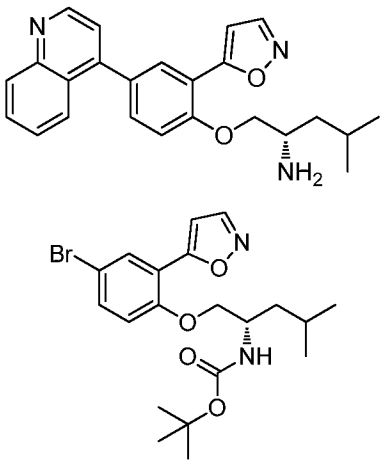
Part B: (S)-2-((2-amino-4-methylpentyl)oxy)-5-(6-methylpyridazin-4-yl)benzonitrile

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. ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{18}H_{23}N_4O$, 311.2]; LC/MS retention time (method B): t_R = 1.46 min.

Example 110

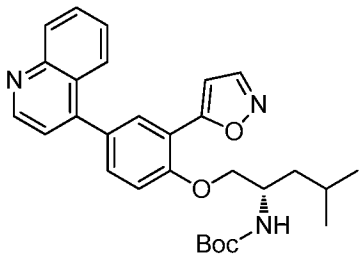
(*S*)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine



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

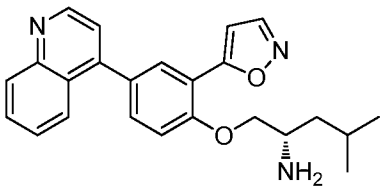
To a 15 mL vial was added (*S*)-*tert*-butyl (1-hydroxy-4-methylpentan-2-yl)carbamate (204 mg, 0.939 mmol), Ph_3P (320 mg, 1.220 mmol), and 4-bromo-2-(isoxazol-5-yl)phenol (225 mg, 0.939 mmol) in tetrahydrofuran (3 mL) to give a tan solution. DIAD (0.256 mL, 1.314 mmol) was added at rt. The resultant clear tan solution was stirred at rt overnight for18h. 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: ^{1}H 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.

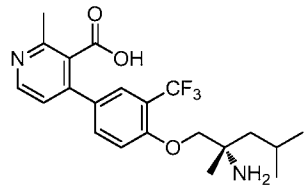


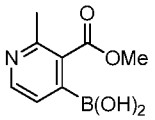
Part C: (S)-1-(2-(isoxazol-5-yl)-4-(quinolin-4-yl)phenoxy)-4-methylpentan-2-amine

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): ^{1}H 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

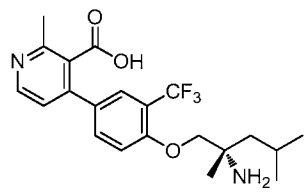
(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-methylnicotinic acid





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

To a vial was added methyl 4-chloro-2-methylnicotinate (52 mg, 0.280 mmol), hypodiboric acid (37.7 mg, 0.420 mmol), 2-(dicyclohexylphosphino))-2',4',6'-triisopropylbiphenyl (2.67 mg, 5.60 µmol), Xphos precatalyst (2.204 mg, 2.80 µmol) 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 with no parent ion. The mixture was directly used in the next step.



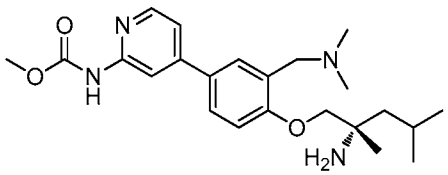
Part B: (S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-2-methylnicotinic acid

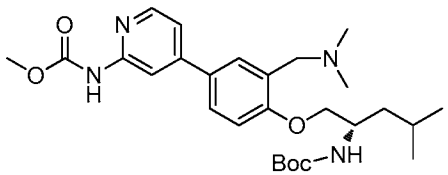
To a 20 mL vial was added (3-(methoxycarbonyl)-2-methylpyridin-4-yl)boronic acid (48.9 mg, 0.251 mmol) (previous reaction vessel) was added potassium phosphate tribasic (2.2 mL, 1.100 mmol). After degassing for 5 min, Xphos precatalyst (4.5 mg, 5.72 µmol) and (*S*)-1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (33 mg, 0.084 mmol) and 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 (18.8 mg, 53%): ^{1}H 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 $C_{21}H_{25}F_3N_2O_3Na$, 433.2]; LC/MS retention time (method C): t_R = 2.60 min.

Example 112

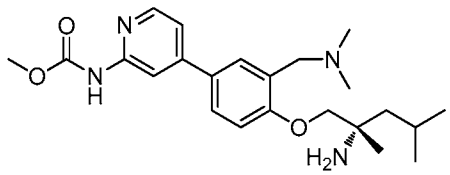
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate





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 (*S*)-methyl (4-(4-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3-carbonylphenyl)pyridin-2-yl)carbamate aldehyde (prepared as described in Example 32, Part G) (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. The layers were separated. The organic layer was washed with brine, dried and concentrated. The tan residue was directly carried onto next reaction.

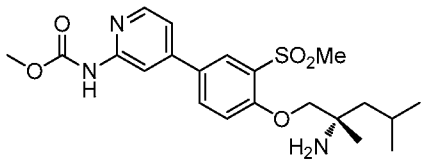


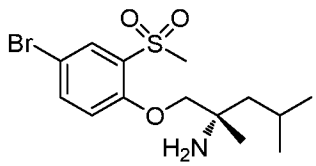
Part B: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-((dimethylamino)methyl)phenyl)pyridin-2-yl)carbamate

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): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{23}H_{35}N_4O_3$, 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

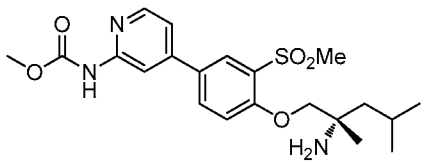




Part A: (S)-1-(4-bromo-2-(methylsulfonyl)phenoxy)-2,4-dimethylpentan-2-amine

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%): ^{1}H 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 - 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 C14H23BrNO$_3$S, 364.1]; LC/MS retention time (method B): t_R = 1.64 min.

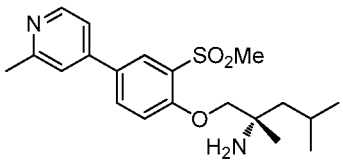


Part B: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(methylsulfonyl)phenyl)pyridin-2-yl)carbamate

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%): ^{1}H 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, 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 C$_{21}$H$_{30}$N$_3$O$_5$S, 436.2]; LC/MS retention time (method B): t_R = 1.52 min.

Example 114

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

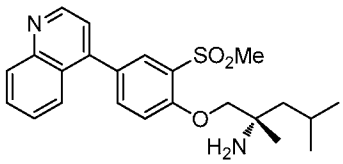


Prepared as described in Example 113 to afford (*S*)-2,4-dimethyl-1-(4-(2-methylpyridin-4-yl)-2-(methylsulfonyl)phenoxy)pentan-2-amine (19 mg, 0.049 mmol, 83%): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.51 (d, *J* = 5.3 Hz, 1H), 8.17 - 8.10 (m, 2H), 7.59 (s, 1H), 7.52 - 7.46 (m, 1H), 7.43 (d, *J* = 9.2 Hz, 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

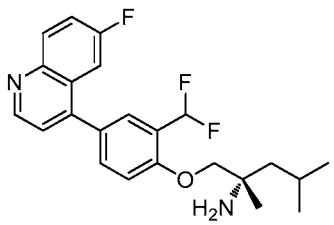
(*S*)-2,4-dimethyl-1-(2-(methylsulfonyl)-4-(quinolin-4-yl)phenoxy)pentan-2-amine

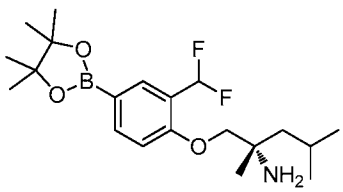


Prepared as described in Example 113 to afford (*S*)-2,4-dimethyl-1-(2-(methylsulfonyl)-4-(quinolin-4-yl)phenoxy)pentan-2-amine (12.2 mg, 0.029 mmol, 58%): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.97 (d, J = 4.4 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.95 - 7.87 (m, 3H), 7.83 (t, J = 7.7 Hz, 1H), 7.65 (t, J = 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.

Example 116

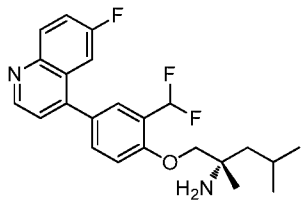
(*S*)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





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. $PdCl_2(dppf)$ (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.

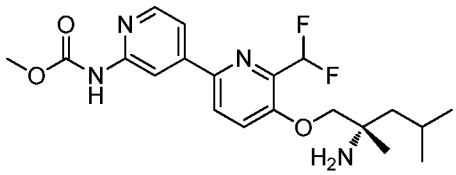


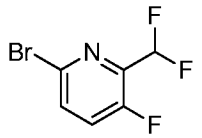
Part B: (S)-1-(2-(difluoromethyl)-4-(6-fluoroquinolin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

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) , Na_2CO_3 (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 (Na_2SO_4), 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-d_6) 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 $C_{23}H_{26}F_3N_2O$, 403.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 117

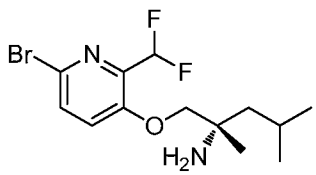
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





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

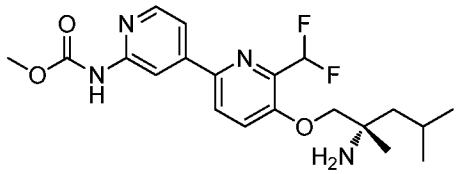
To a 100 mL round-bottomed flask was added 6-bromo-3-fluoropicolinaldehyde (459.8 mg, 2.254 mmol) in CH_2Cl_2 (10 mL) to give a tan solution. After cooling to -20 °C, DAST (0.596 mL, 4.51 mmol) was added dropwise under nitrogen. The mixture was gradually warmed up to rt. The mixture was stirred at rt for 3 h. TLC (3/1 hexane/EtOAc) showed complete conversion to a less polar spot. The reaction was slowly quenched by saturated $NaHCO_3$ 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: ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -116.97, -127.89.



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 EtOAc. The combined organic solution was washed with brine, dried and concentrated to a tan oil (338 mg, 94%): ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -117.98.; LCMS (ESI) *m/e* 336.9 [(M+H)$^+$, calcd $C_{13}H_{20}BrF_2N_2O$, 337.1]; LC/MS retention time (method B): t_R = 1.67 min.

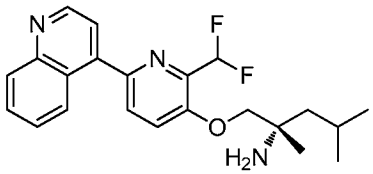


Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

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 Na_2CO_3 (0.126 mL, 0.253 mmol) in dioxane (0.6 mL) to give a colorless suspension 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 Na_2SO_4. The organic solution was concentrated. The residue was purified twice by prep-HPLC to afford (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (12.6 mg, 37%): ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{20}H_{27}F_2N_4O_3$, 409.2]; LC/MS retention time (method B): t_R = 1.66 min.

Example 118

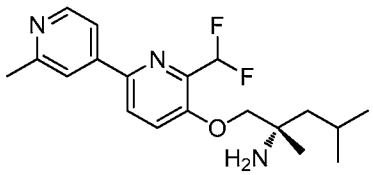
(*S*)-1-((2-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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): ^{1}H 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 $C_{22}H_{26}F_2N_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.54 min.

Example 119

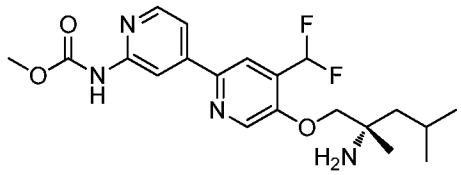
(*S*)-1-((6-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

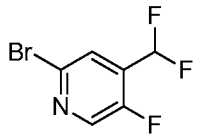


Prepared as described in Example 117 to afford (*S*)-1-((6-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (18.3 mg, 0.051 mmol, 92% yield for three steps): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.54 (d, *J* = 5.2 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.90 (s, 1H), 7.82 (d, *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 $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method B): t_R = 1.45 min.

Example 120

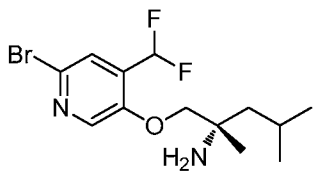
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





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

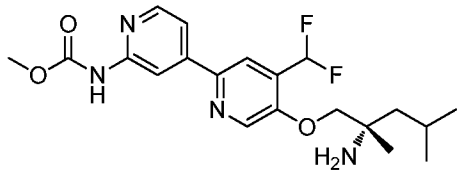
To a 100 mL round-bottomed flask was added 2-bromo-5-fluoroisonicotinaldehyde (605 mg, 2.97 mmol) in CH_2Cl_2 (12 mL) to give a tan solution. After cooling to -20 °C, DAST (0.705 mL, 5.34 mmol) was added dropwise under nitrogen. The mixture was gradually warmed up to rt. The mixture was stirred at rt 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: ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -117.92 , -135.51.



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 organic solution was washed with brine, dried and concentrated to a tan oil (361 mg, 96%): ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -119.58; LCMS (ESI) *m/e* 336.9 [(M+H)$^+$, calcd $C_{13}H_{20}BrF_2N_2O$, 337.1]; LC/MS retention time (method B): t_R = 1.79 min.

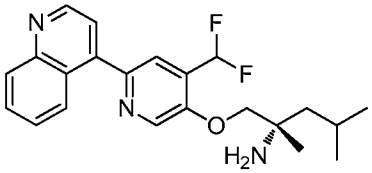


Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

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): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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), 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 $C_{20}H_{27}F_2N_4O_3$, 409.2]; LC/MS retention time (method B): t_R = 1.66 min.

Example 121

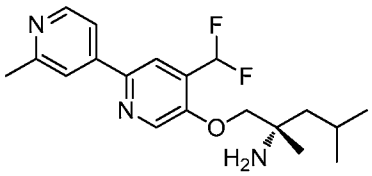
(*S*)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{22}H_{26}F_2N_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.58 min.

Example 122

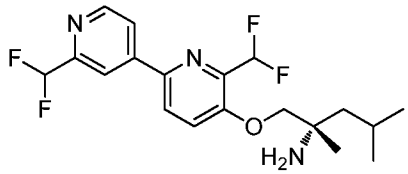
(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

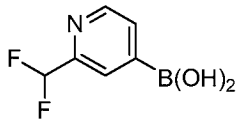


Prepared as described in Example 117 to afford (*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (13.6 mg, 0.039 mmol, 74% yield for three steps): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.68 (s, 1H), 8.54 (d, *J* = 5.3 Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.84 (d, *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 $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method B): t_R = 1.46 min.

Example 123

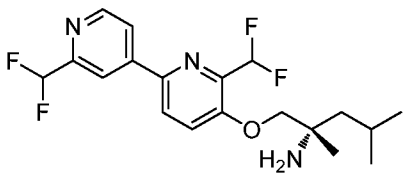
(*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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-(dicyclohexylphosphino))-2',4',6'-triisopropylbiphenyl (8.58 mg, 0.018 mmol), Xphos precatalyst (7.08 mg, 9.00 μmol) 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 of different reactions.



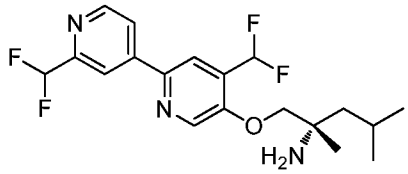
Part B: (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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 μmol) and (*S*)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (26.5 mg, 0.079 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 (29.8 mg, 98%) as a colorless solid. ^{1}H 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 [(M+H)$^+$, calcd $C_{19}H_{24}F_4N_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.85 min.

Example 124

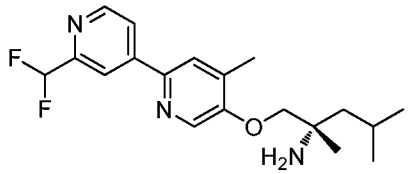
(*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

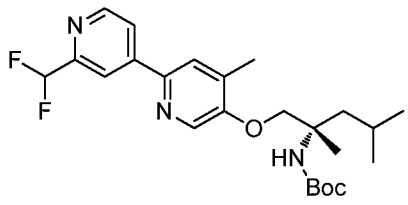


Prepared as described in Example 123 to afford (*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (25.9 mg, 0.067 mmol, 77% yield) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.79 (d, J = 5.2 Hz, 1H), 8.71 (s, 1H), 8.36 (s, 1H), 8.32 (s, 1H), 8.25 (d, 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 [(M+H)$^+$, calcd $C_{19}H_{24}F_4N_3O$, 386.2]; LC/MS retention time (method B): t_R = 1.83 min.

Example 125

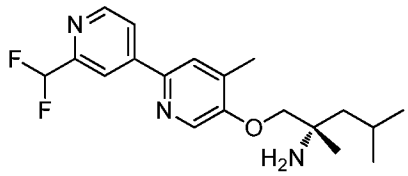
(*S*)-1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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. ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -115.81; LCMS (ESI) *m/e* 450.1 [(M+H)$^+$, calcd $C_{24}H_{34}F_2N_3O_3$, 450.2]; LC/MS retention time (method B): t_R = 2.31 min.

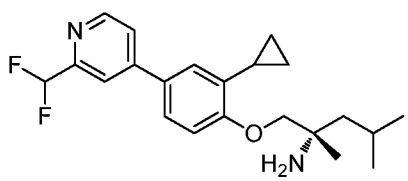


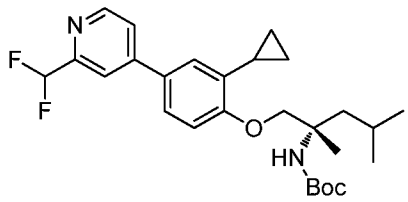
Part B: (S)-1-((2'-(difluoromethyl)-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7, Part B (34.9 mg, 100%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -115.37 (d, *J* = 54.8 Hz); LCMS (ESI) *m/e* 350.0 [(M+H)$^+$, calcd $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method B): t_R = 1.80 min.

Example 126

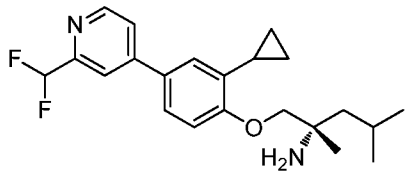
(*S*)-1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





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. ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -115.77; LCMS (ESI) *m/e* 475.0 [(M+H)$^+$, calcd $C_{27}H_{37}F_2N_2O_3$, 475.3]; LC/MS retention time (method B): t_R = 2.48 min.

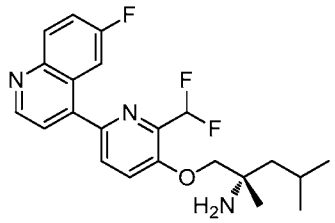


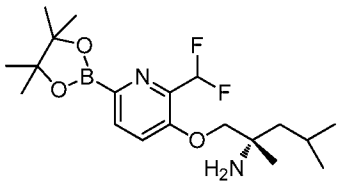
Part B: (S)-1-(2-cyclopropyl-4-(2-(difluoromethyl)pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7, Part B (25.8 mg, 100%) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -115.05 (d, *J* = 54.9 Hz); LCMS (ESI) *m/e* 375.0 [(M+H)$^+$, calcd $C_{22}H_{29}F_2N_2O$, 375.2]; LC/MS retention time (method B): t_R = 1.97 min.

Example 127

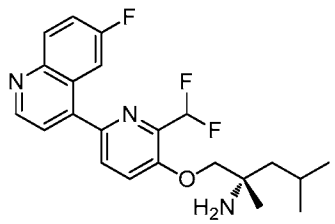
(*S*)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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. $PdCl_2(dppf)$ (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.



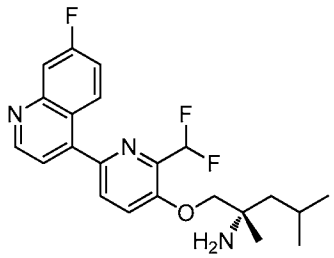
Part B: (S)-1-((2-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 118 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 $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.81 min.

Example 128

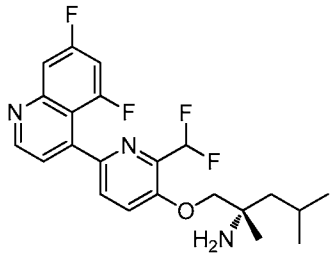
(*S*)-1-((2-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 118 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. ^{1}H 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, 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 = 1.68 min.

Example 129

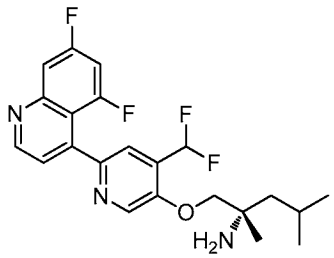
(*S*)-1-((2-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

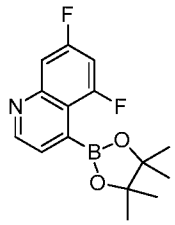


Prepared as previously described in Example 118 to afford (*S*)-1-((2-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (25.9 mg, 75% for 2 steps) as a colorless solid. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 9.13 - 9.02 (m, 1H), 7.93 - 7.73 (m, 3H), 7.56 (dt, *J* = 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.

Example 130

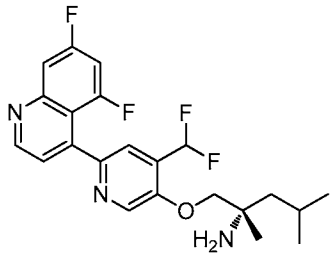
(*S*)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 and used directly in the next step. LC/MS retention time (method A): t_R = 1.93 min.

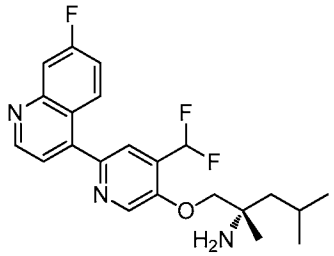


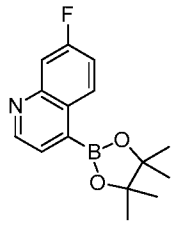
Part B: (S)-1-((4-(difluoromethyl)-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 121 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. ^{1}H 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 $C_{22}H_{24}F_4N_3O$, 422.2]; LC/MS retention time (method B): t_R = 1.88 min.

Example 131

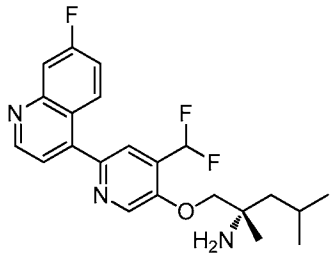
(*S*)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 and used directly in the next step. LC/MS retention time (method A): t_R = 1.19 min.

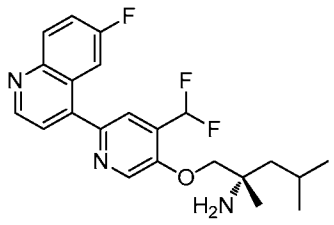


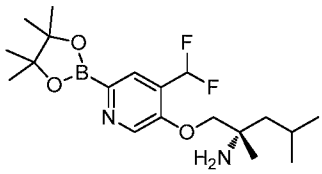
Part B: (S)-1-((4-(difluoromethyl)-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 121 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. ^{1}H 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 (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.

Example 132

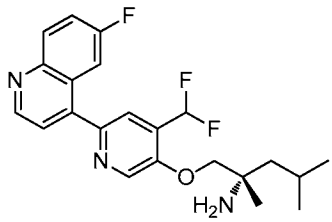
(*S*)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 μmol) 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.



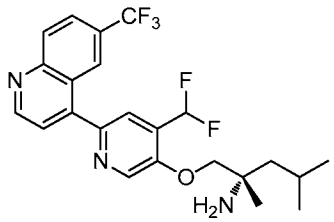
Part B: (S)-1-((4-(difluoromethyl)-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 121 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 $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.79 min.

Example 133

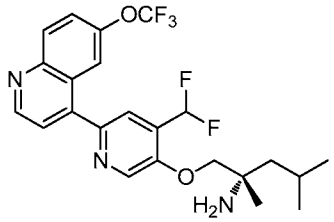
((*S*)-1-((4-(difluoromethyl)-6-(6-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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

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

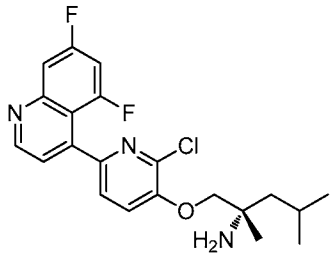


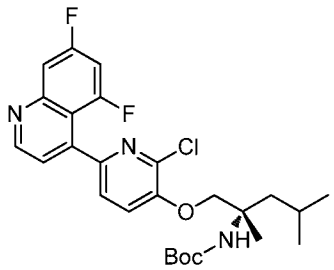
Prepared as previously described in Example 132 to afford (*S*)-1-((4-(difluoromethyl)-6-(6-(trifluoromethoxy)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (1.5 mg, 4% for 2 steps) as a colorless solid. ^{1}H NMR (600

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 [$(M+H)^+$, calcd $C_{23}H_{25}F_5N_3O_2$, 470.2]; LC/MS retention time (method B): t_R = 2.00 min.

Example 135

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

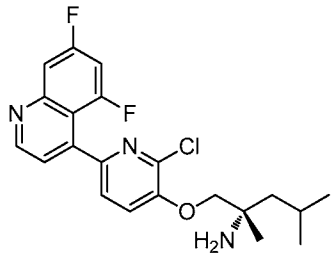




Part A: (S)-tert-butyl (1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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-yl)carbamate (12.1 mg, 34%) as a colorless solid. ^{1}H 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);^{19}F NMR

(376 MHz, Chloroform-d) δ -102.47 , -107.56.; LCMS (ESI) *m/e* 506.0 [(M+H)$^+$, calcd $C_{26}H_{31}ClF_2N_3O_3$, 506.2]; LC/MS retention time (method B): t_R = 2.36 min.

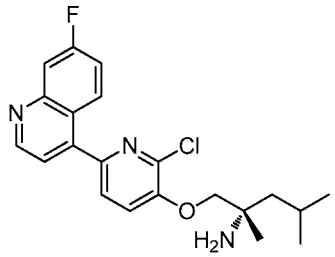


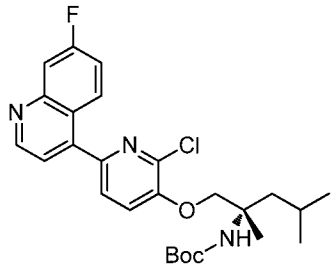
Part B: (S)-1-((2-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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. ^{1}H 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; ^{19}F 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

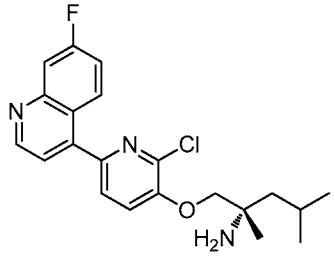
(*S*)-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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. ^{1}H 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.



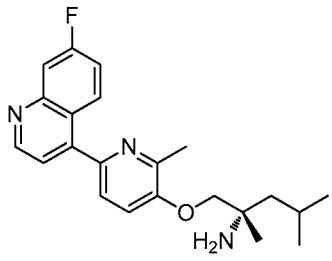
Part B: (S)-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

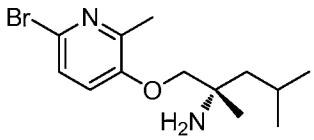
Prepared as previously described in Example 7, Part B to afford (*S*)-1-((2-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (11.1 mg, 100%) as a colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (d, *J* = 4.4 Hz, 1H), 8.32 (dd, *J* = 9.4, 6.1 Hz, 1H), 7.88 - 7.77 (m, 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 $C_{21}H_{24}ClFN_3O$, 388.2]; LC/MS retention time (method B): t_R = 1.76 min.

Example 137

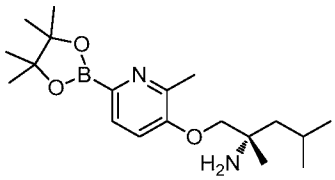
(S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





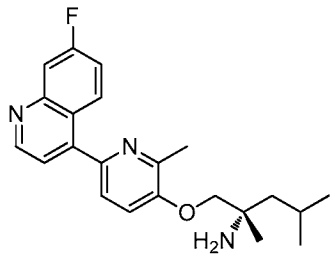
Part A: (S)-1-((6-bromo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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 NH_3) in CH_2Cl_2 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 $[(M-NH_2)^+$, calcd $C_{13}H_{19}BrNO$, 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. $PdCl_2(dppf)$ (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.

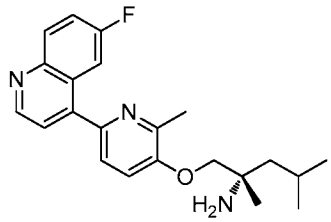


Part C: (S)-1-((6-(7-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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-d_6) 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 $C_{22}H_{27}FN_3O$, 368.2]

Example 138

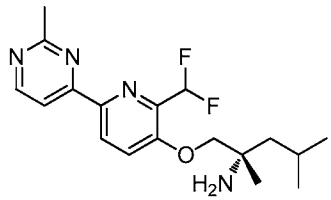
(*S*)-1-((6-(6-fluoroquinolin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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): ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{22}H_{27}FN_3O$, 368.2].

Example 139

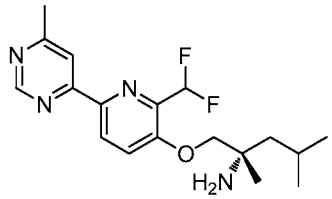
(*S*)-1-((2-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 127 with intermediate as described in Example 127 and 4-bromo-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%): ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{18}H_{24}F_2N_4NaO$, 373.2]; LC/MS retention time (method B): t_R = 1.73 min.

Example 140

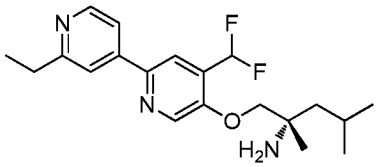
(*S*)-1-((2-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H 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-NH_2)$^+$, calcd $C_{18}H_{22}F_2N_3O$, 334.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 141

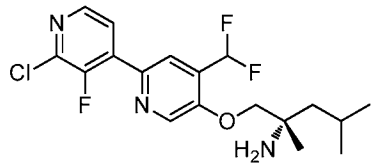
(*S*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-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%): ^{1}H 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 $C_{20}H_{28}F_2N_3O$, 364.2]; LC/MS retention time (method B): t_R = 1.54 min.

Example 142

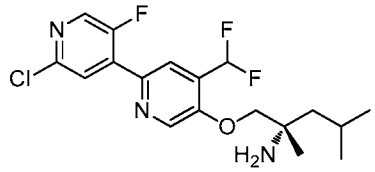
(*S*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H 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-NH$_2$)$^+$, calcd C$_{18}$H$_{19}$ClF$_3$N$_2$O, 371.1]; LC/MS retention time (method B): t_R = 1.98 min.

Example 143

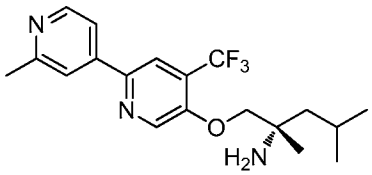
(*S*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

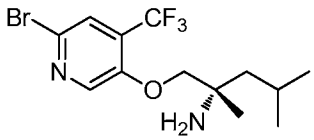


Prepared as previously described in Example 117 with intermediate as described in Example 120 and (2-chloro-5-fluoro-pyridin-4-yl)boronic acid to afford (*S*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (9.6 mg, 11%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd C$_{18}$H$_{19}$ClF$_3$N$_2$O, 371.1]; LC/MS retention time (method B): t_R = 1.97 min.

Example 144

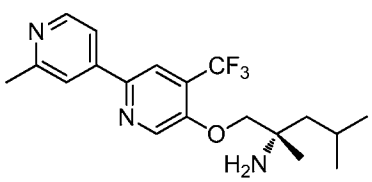
(*S*)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine





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/CH_2Cl_2 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: ^{1}H 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 [$(M+H)^+$, calcd $C_{13}H_{16}BrF_3NO$, 338.1]; LC/MS retention time (method B): t_R = 1.88 min.

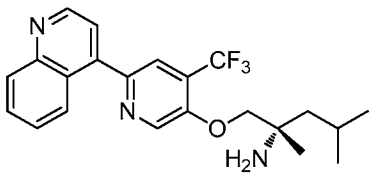


Part B: (S)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine

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): ^{1}H 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 $(M+H)^+$, calcd $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.48 min.

Example 145

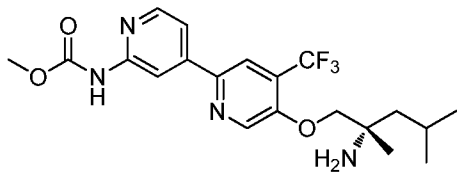
(*S*)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine



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): ^{1}H 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, *J* = 6.1 Hz, 6H); LCMS (ESI) *m/e* 404.2 $(M+H)^+$, calcd $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.71 min.

Example 146

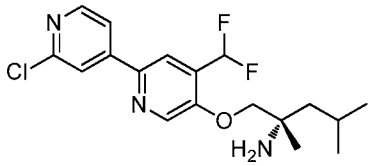
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate



Prepared as described in Example 117 to afford (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (4.4 mg, 0.010 mmol, 18% yield): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{20}H_{25}F_3N_4NaO_3$, 449.2]; LC/MS retention time (method B): t_R = 1.79 min.

Example 147

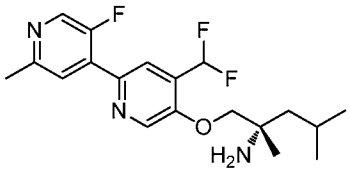
(*S*)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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 (13.5 mg, 53%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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

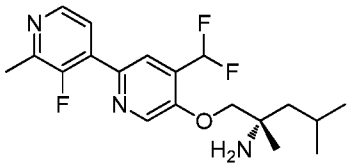
(*S*)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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 168) (7.42 mg, 0.019 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (2.402 mg, 0.019 mmol), and Cs_2CO_3 (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%): ^{1}H NMR (500 MHz, DMSO-d_6) 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

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

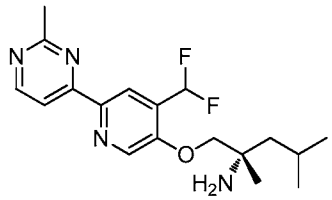


Prepared as previously described in Example 148 with Example 142 as the starting material to afford (*S*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (2.0 mg, 25%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.39 (d, *J* = 5.1 Hz, 1H), 8.01 (s, 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-NH_2)$^+$, calcd $C_{19}H_{22}F_3N_2O$, 351.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 150

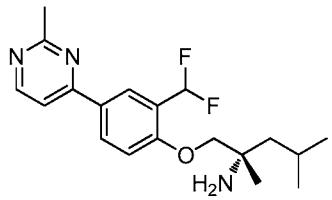
(*S*)-1-((4-(difluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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. ^{1}H 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-NH_2)$^+$, calcd $C_{18}H_{22}F_2N_3O$, 334.2]; LC/MS retention time (method B): t_R = 1.83 min.

Example 152

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

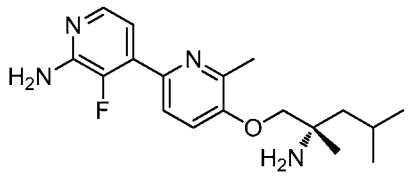


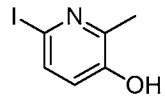
Prepared as previously described in Example 116 with 4-bromo-2-methylpyrimidine to afford (*S*)-1-(2-(difluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (32.2 mg, 56% for 2 steps) as a colorless solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, J = 5.4 Hz, 1H), 8.38 (d, J = 2.2 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-NH_2)$^+$, calcd $C_{19}H_{23}F_2N_2O$, 333.2]; LC/MS retention time (method B): t_R = 1.85 min.

Example 153

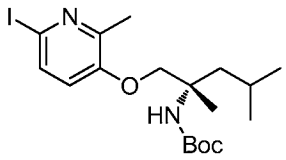
(*S*)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine





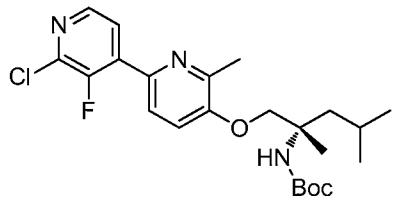
Part A: 6-iodo-2-methylpyridin-3-ol

To a 500 mL round-bottomed flask was added 2-methylpyridin-3-ol (4.0 g, 36.7 mmol) and Na_2CO_3 (7.8 g, 73.6 mmol) in water (100 mL) to give a slightly tan solution/suspension. I_2 (9.6 g, 37.8 mmol) was added in one portion. The mixture was stirred at rt for 3 h. There were noticeable I_2 left. The mixture was stirred overnight and there was still I_2 left. The reaction mixture was heated at 42 °C (bath temp) for 5 h (most I_2 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: ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (dd, J = 8.3, 0.7 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 2.48 (s, 3H); LCMS (ESI) m/e 235.8 [(M+H)$^+$, calcd C_6H_7INO, 236.0]; LC/MS retention time (method B): t_R = 1.14 min.



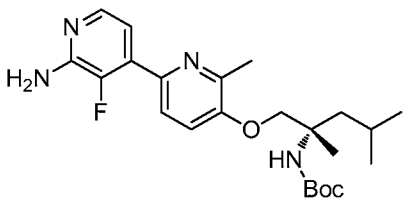
Part B: (S)-tert-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2 yl)carbamate

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: ^{1}H 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 $C_{18}H_{30}IN_2O_3$, 449.1]; LC/MS retention time (method B): t_R = 2.38 min.



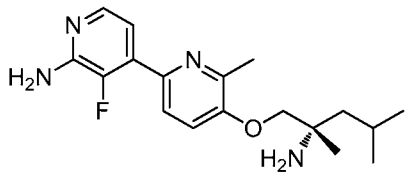
Part C: (S)-tert-butyl (1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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 $C_{23}H_{32}ClFN_3O_3$, 452.2]; LC/MS retention time (method B): t_R = 2.46 min.



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, $PdOAc_2$ (0.939 mg, 4.18 μmol), XANTPHOS (4.84 mg, 8.36 μmol), Cs_2CO_3 (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 $C_{23}H_{34}FN_4O_3$, 433.3]; LC/MS retention time (method B): t_R = 1.99 min; The chloride: 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 = 2.48 min.

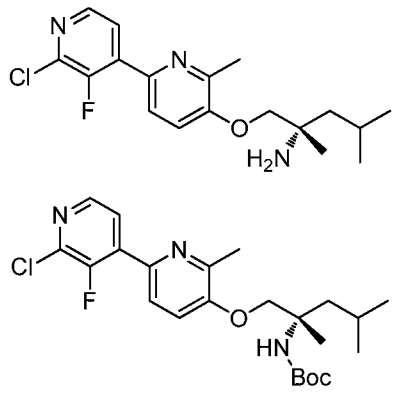


Part E: (S)-5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-amine

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): ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{18}H_{26}FN_4O$, 333.2]; LC/MS retention time (method B): t_R = 1.48 min.

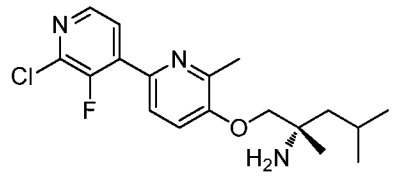
Example 154

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



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 $C_{23}H_{32}ClFN_3O_3$, 452.2]; LC/MS retention time (method B): t_R = 2.48 min.

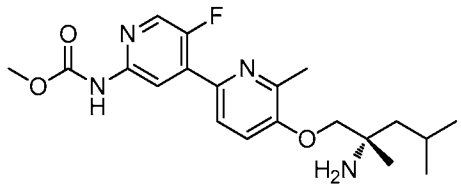


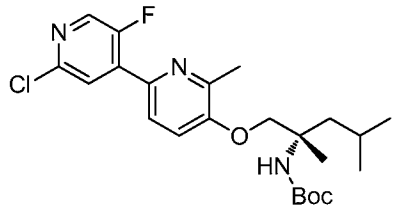
Part B: (S)-1-((2'-chloro-3'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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): ^{1}H NMR (500 MHz, DMSO-d_6) 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.

Example 155

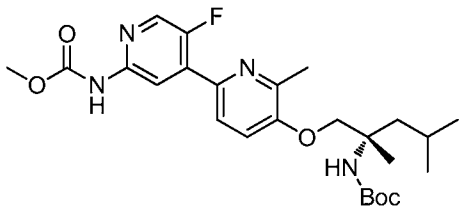
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate





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

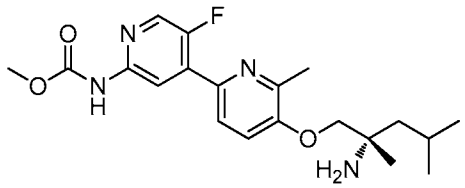
Prepared as previously described in Example 66 with intermediate from Example 153 and (2-chloro-5-fluoro-pyridin-4yl)boronic acid to afford (*S*)-*tert*-butyl (1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (13.4 mg, 13%): LCMS (ESI) *m/e* 452.1 [$(M+H)^+$, calcd $C_{23}H_{32}ClFN_3O_3$, 452.2]; LC/MS retention time (method B): t_R = 2.49 min.



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 $C_{25}H_{36}FN_4O_5$, 491.3]; LC/MS retention time (method B): t_R = 2.30 min.

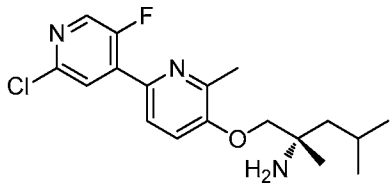


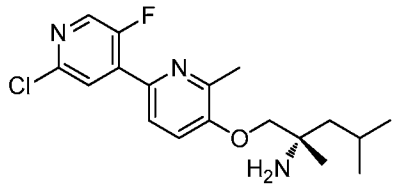
Part C: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-5'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

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. ^{1}H NMR (400 MHz, Methanol-d_4) 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 $C_{20}H_{28}FN_4O_3$, 391.2].

Example 156

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



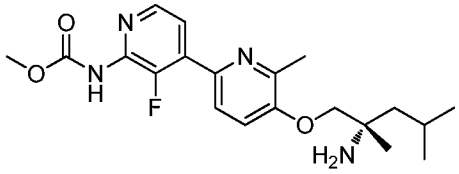


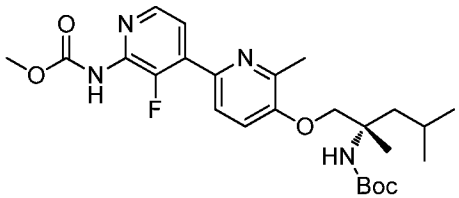
Part C: (S)-1-((2'-chloro-5'-fluoro-6-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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. ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 (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-NH$_2$)$^+$, calcd $C_{18}H_{21}ClFN_2O$, 335.1]; LC/MS retention time (method B): t_R = 1.93 min.

Example 157

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

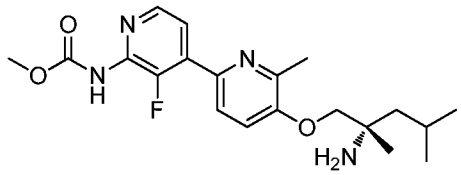




Part A: (S)-methyl (5-((2-Boc-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described in Example 153 with reaction running at 80 °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 $C_{25}H_{36}FN_4O_5$, 491.3]; LC/MS retention time (method A): t_R = 1.99 min.

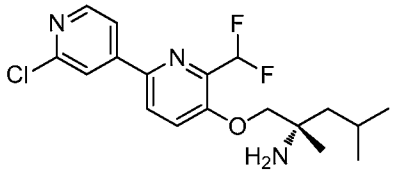


Part B: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-3'-fluoro-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate

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%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.25 (d, *J* = 5.1 Hz, 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 $C_{20}H_{27}FN_4NaO_3$, 413.2]; LC/MS retention time (method B): t_R = 1.66 min.

Example 158

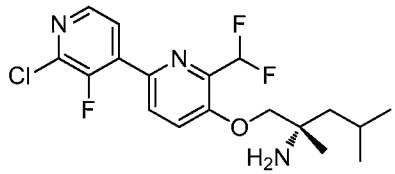
(*S*)-1-((2'-chloro-6-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H NMR (500 MHz, DMSO-d_6) 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 $C_{19}H_{26}F_2N_3O$, 370.1]; LC/MS retention time (method B): t_R = 1.91 min.

Example 159

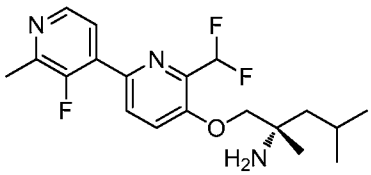
(*S*)-1-((2'-chloro-6-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{18}H_{22}ClF_3N_3O$, 388.1]; LC/MS retention time (method B): t_R = 1.94 min.

Example 160

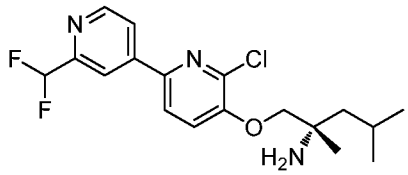
(*S*)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

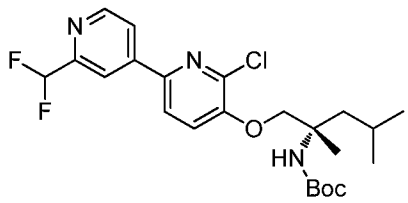


Prepared as described in Example 148 to afford (*S*)-1-((6-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (12.8 mg, 0.033 mmol, 55%): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.39 (d, *J* = 5.0 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.9 Hz, 1H), 7.75 (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 $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.72 min.

Example 161

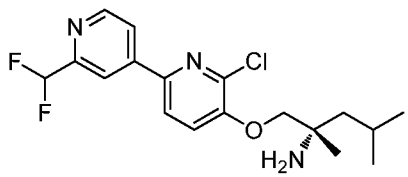
((*S*)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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%): ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -115.83; LCMS (ESI) *m/e* 470.2 $(M+H)^+$, calcd $C_{23}H_{31}ClF_2N_3O_3$, 470.2]; LC/MS retention time (method A): t_R = 2.50 min.

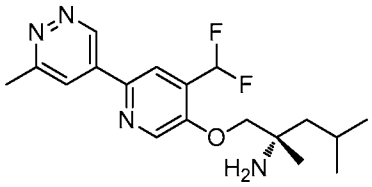


Part B: ((S)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

Prepared as previously described in Example 7 to afford ((*S*)-1-((6-chloro-2'-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (40.6 mg, 74%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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); ^{19}F NMR (376 MHz, DMSO-d6) δ -115.46 (d, *J* = 55.0 Hz); LCMS (ESI) *m/e* 392.1 [(M+Na)$^+$, calcd $C_{18}H_{22}ClF_2N_3NaO$, 392.1]; LC/MS retention time (method B): t_R = 1.94 min.

Example 162

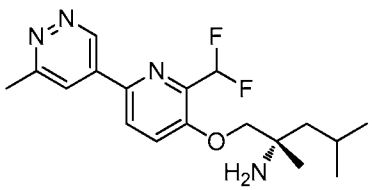
(*S*)-1-((4-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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 $C_{18}H_{24}F_2N_4NaO$, 373.2]; LC/MS retention time (method B): t_R = 1.59 min.

Example 163

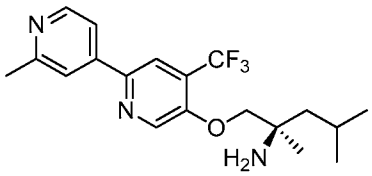
(*S*)-1-((2-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

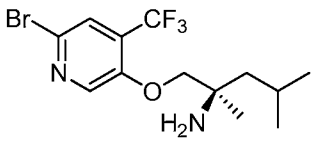


Prepared as described in Example 117 with 3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine to afford (*S*)-1-((2-(difluoromethyl)-6-(6-methylpyridazin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (37.2 mg, 0.105 mmol, 85%): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.71 (d, *J* = 2.1 Hz, 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 $C_{18}H_{24}F_2N_4NaO$, 373.2]; LC/MS retention time (method B): t_R = 1.62 min.

Example 164

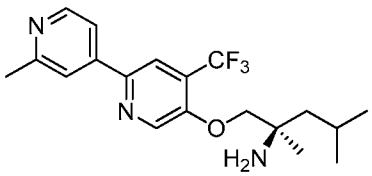
(*R*)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine





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: ^{1}H 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 [(M+H)$^+$, calcd $C_{13}H_{16}BrF_3NO$, 338.1]; LC/MS retention time (method B): t_R = 1.87 min.

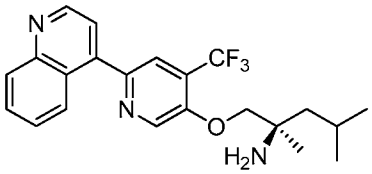


Part B: (R)-2,4-dimethyl-1-((2'-methyl-4-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine

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): ^{1}H 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 $(M+H)^+$, calcd $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.44 min.

Example 165

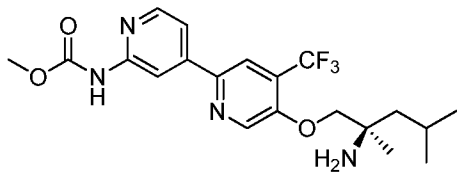
(*R*)-2,4-dimethyl-1-((6-(quinolin-4-yl)-4-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine



Prepared as described in Example 145 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): ^{1}H 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 $(M+H)^+$, calcd $C_{22}H_{25}F_3N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.66 min.

Example 166

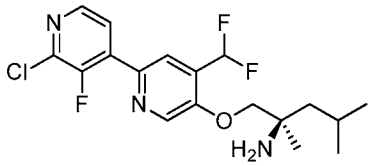
(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

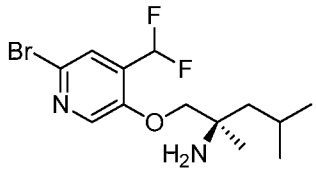


Prepared as described in Example 144 to afford (*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-(trifluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (7.8 mg, 0.018 mmol, 35% yield): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.81 (s, 1H), 8.54 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.18 (s, 1H), 7.74 (dd, *J* = 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), 0.92 (dd, *J* = 6.8, 2.7 Hz, 6H); LCMS (ESI) *m/e* 449.1 $(M+Na)^+$, calcd $C_{20}H_{25}F_3N_4NaO_3$, 449.2]; LC/MS retention time (method B): t_R = 1.72 min.

Example 167

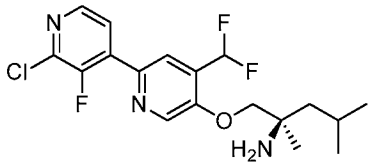
(*R*)-1-((2'-chloro-4-(difluoromethyl)-3'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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

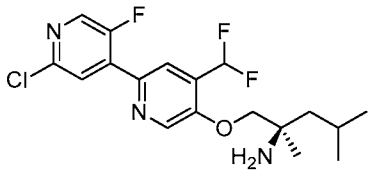
Prepared as previously described in Example 142 with *R*-enantiomer of the amino alcohol to afford (*R*)-1-((6-bromo-4-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (740 mg, 95%): LCMS (ESI) *m/e* 336.9 $[(M+H)^+$, calcd $C_{13}H_{20}BrF_2N_2O$, 337.1]; LC/MS retention time (method B): t_R = 1.83 min. The 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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd $C_{18}H_{19}ClF_3N_2O$, 371.1]; LC/MS retention time (method B): t_R = 2.02 min.

Example 168

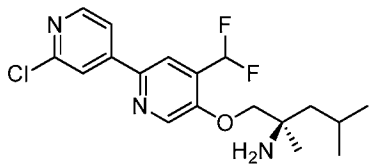
(*R*)-1-((2'-chloro-4-(difluoromethyl)-5'-fluoro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd $C_{18}H_{19}ClF_3N_2O$, 371.1]; LC/MS retention time (method B): t_R = 1.98 min.

Example 169

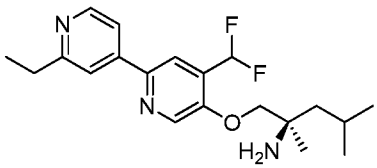
(*R*)-1-((2'-chloro-4-(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 142 with intermediate as described in Example 167 and (2-chloro-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%): ^{1}H 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-NH$_2$)$^+$, calcd $C_{18}H_{20}ClF_2N_2O$, 353.1]; LC/MS retention time (method B): t_R = 1.90 min.

Example 170

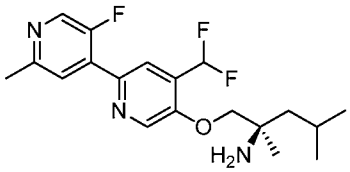
(*R*)-1-((4-(difluoromethyl)-2'-ethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H 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 $C_{20}H_{28}F_2N_3O$, 364.2]; LC/MS retention time (method B): t_R = 1.48 min.

Example 171

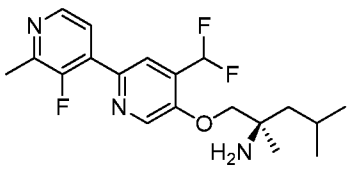
(*R*)-1-((4-(difluoromethyl)-5'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as previously described in Example 148 with Example 168 as the starting material 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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd $C_{19}H_{22}F_3N_2O$, 351.2]; LC/MS retention time (method B): t_R = 1.80 min.

Example 172

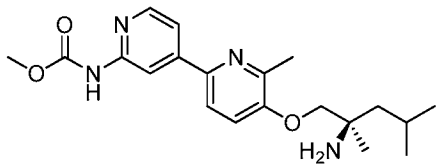
(*R*)-1-((4-(difluoromethyl)-3'-fluoro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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%): ^{1}H NMR (500 MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd $C_{19}H_{22}F_3N_2O$, 351.2]; LC/MS retention time (method B): t_R = 1.79 min.

Example 173

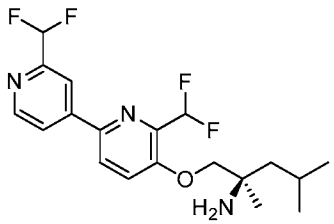
(*R*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate



Prepared as previously described in Example 64 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. ^{1}H NMR (400MHz, MeOH-d_4) 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 $C_{20}H_{29}N_4O_3$, 373.2]; LC/MS retention time (method D): t_R = 1.81 min.

Example 174

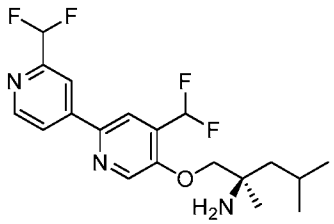
(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (500MHz, DMSO-d_6) 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

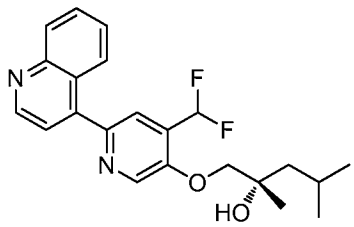
(*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

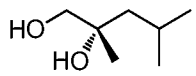


Prepared as previously described in Example 124 using the *R*-enantiomer of the amino alcohol to afford (*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (9.3 mg, 0.024 mmol, 21%) as a film. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.79 (d, *J*=5.1 Hz, 1H), 8.71 (s, 1H), 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

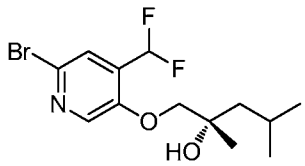




Part A: (S)-2,4-dimethylpentane-1,2-diol

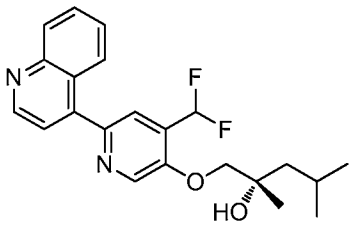
To a 500 mL round-bottomed flask was added AD-MIX-ALPHA (3.60 g, 2.60 mmol) in BuOH (13 mL) and water (13 mL) to give a yellow solution under vigorously stirring. The resulting mixture was stirred at rt for 30 min and then cooled to 0 °C. A precipitate appeared and 2,4-dimethylpent-1-ene (0.364 mL, 2.60 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. CH_2Cl_2 (40 mL) and water (80 mL) was then

added successively and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2. 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: ^{1}H 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

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 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 $C_{13}H_{19}BrF_2NO_2$, 338.0]; LC/MS retention time (method B): t_R = 2.30 min.



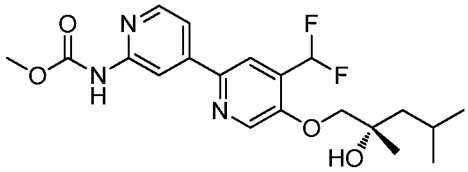
Part C: (S)-1-((4-(difluoromethyl)-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-ol

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%): ^{1}H 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, 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 $C_{22}H_{25}F_2N_2O_2$, 387.2]; LC/MS retention time (method B): t_R = 2.06 min.

Example 177

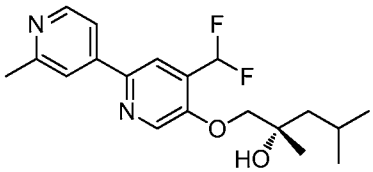
(*S*)-methyl (4-(difluoromethyl)-5-((2-hydroxy-2,4-dimethylpentyl)oxy)-[2,4'-bipyridin]-2'-yl)carbamate



Prepared as previously described in Example 117 with intermediate from Example 176 (1.8 mg, 6.5%): ^{1}H 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 $C_{20}H_{26}F_2N_3O_4$, 410.2]; LC/MS retention time (method B): t_R = 2.07 min.

Example 178

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

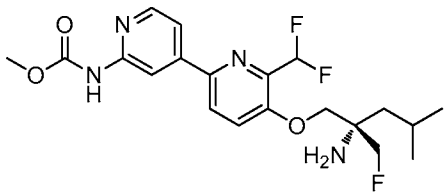


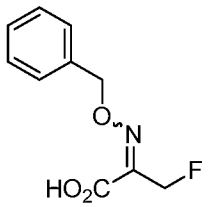
Prepared as previously described in Example 117 with intermediate from Example 176 to afford (*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-ol (2.2 mg, 7.2%): ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.54 (d, J = 5.3 Hz, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.84 (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 $C_{19}H_{25}F_2N_2O_2$, 351.2]; LC/MS retention time (method B): t_R = 1.91 min.

Example 179

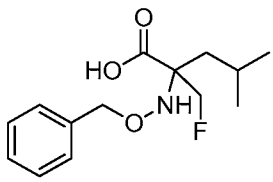
(*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





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 ¼ ratio). The material was used as is.



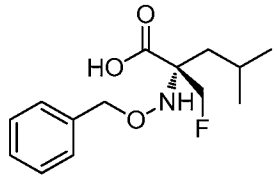
Part B: 2-((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid

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 NH_4Cl (50 mL) to give a tan solution.

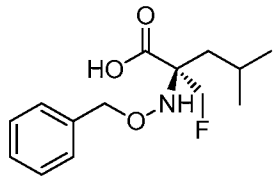
Zinc (3.59 g, 54.9 mmol) was added portionwise. The mixture was stirred at rt for 30 min. The mixture was diluted with water and EtOAc. The layers were separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried and concentrated to a dense semi-solid. 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/CH_2Cl_2 (Rf~0.3) afforded 2-((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid (2.33 g, 76%) as a white solid: ^{1}H 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -233.34; LCMS (ESI) *m/e* 290.1 [$(M+Na)^+$, calcd $C_{14}H_{18}FNNaO_3$, 290.1]; LC/MS retention time (method B): t_R = 2.04 min.

The racmeic compound (2 g) was separated by chiral super critical fluid chromatography (Column: ChiralPak AD-H, 30 x 250mm, 5µm); Mobile Phase: 10 % EtOH / 90% CO_2 to give the two enantiomers.

Analytical super critical fluid chromatography conditions: Column: ChiralPak 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% CO_2; Detector Wavelength: UV 205 nm.

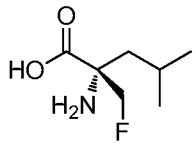


Enantiomer 1 (0.9 g, 90% recovery, e.e.% > 99.9%, α_D = +7.87° ($CHCl_3$, 3.05 mg/ml)): (*S*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 3.00 min.



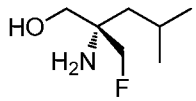
Enantiomer 2 (0.9 g, 90% recovery, e.e.% = 92.6%, α_D = -9.20° ($CHCl_3$, 3.15 mg/ml)): (*R*)-benzyl 4-methyl-4-(2-methylallyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide HPLC retention time = 3.52 min.

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).



Part C: (S)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid

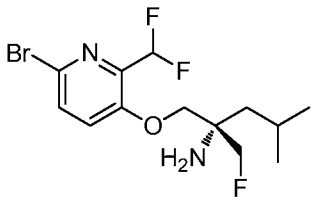
To a 1 L round-bottomed flask was added (*S*)-2-((benzyloxy)amino)-2-(fluoromethyl)-4-methylpent-4-enoic acid (0.89 g, 3.33 mmol) in MeOH (30 mL) to give a colorless solution. Pd-C (0.709 g, 0.666 mmol) was added. The mixture was stirred under hydrogen (balloon) for 16 h. LCMS showed complete disappearance 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: ^{1}H 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); ^{19}F NMR (376 MHz, Methanol-d4) δ -229.19; α_D = +21.61° (MeOH, 2.85 mg/mL).



Part D: (S)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol

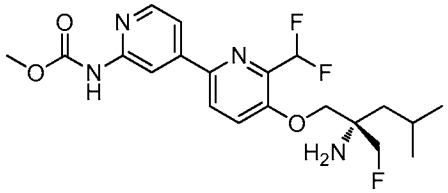
To a 250 mL round-bottomed flask was added (*S*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid (496 mg, 3.04 mmol) in tetrahydrofuran (15 mL) to give a colorless solution under nitrogen. BH_3.THF (12.16 mL, 12.16 mmol) was added under nitrogen. The mixture was stirred at rt over the weekend for 66 h. TLC showed (10% MeOH/$CH2Cl_2$, I_2 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 CH_2Cl_2. 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: ^{1}H 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, 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; α_D = -1.00° ($CHCl_3$, 2.40 mg/mL).



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%): ^{1}H 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 [(M+H)$^+$, calcd $C_{13}H_{19}BrF_3N_2O$, 355.1]; LC/MS retention time (method B): t_R = 1.69 min.

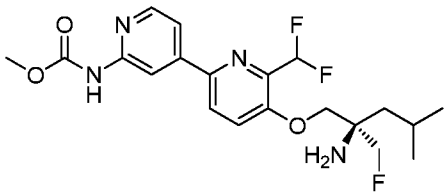


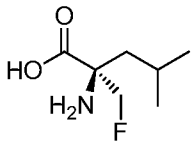
Part F. (S)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described for Example 117 but at 80 °C for 5 h to afford the titled product (9.7 mg, 36%): ^{1}H 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 $C_{20}H_{26}F_3N_4O_3$, 427.2]; LC/MS retention time (method B): t_R = 1.66 min.

Example 180

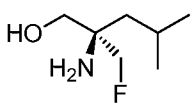
(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





Part A: (*R*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid

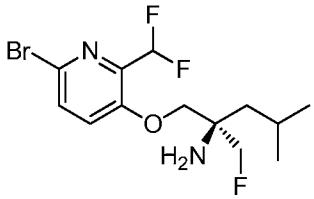
Prepared as previously described in Example 179, Part C to afford (*R*)-2-amino-2-(fluoromethyl)-4-methylpentanoic acid (512 mg, 94%) as a white solid: ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.62 (ddd, *J* = 62.0, 47.4, 10.0 Hz, 2H), 1.94 - 1.66 (m, 3H), 1.01 (dd, *J* = 6.3, 3.9 Hz, 6H); ^{19}F NMR (376 MHz, Methanol-d4) δ -229.19; α_D = -20.29° (MeOH, 2.70 mg/mL).



Part B: (R)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol

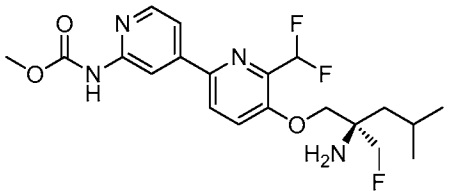
Prepared as previously described in Example 179, Part D to afford (*R*)-2-amino-2-(fluoromethyl)-4-methylpentan-1-ol (362 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, Methanol-d$_4$) δ 4.31 (d, *J* = 47.7 Hz, 2H), 3.53 (dd, *J* = 10.8, 1.3

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; α_D = +1.11° ($CHCl_3$, 2.70 mg/mL).



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: ^{1}H NMR (400 MHz, Methanol-d4) 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 [$(M+H)^+$, calcd $C_{13}H_{19}BrF_3N_2O$, 355.1]; LC/MS retention time (method B): t_R = 1.68 min.



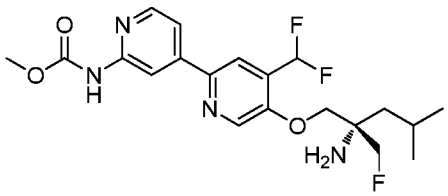
Part D: (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

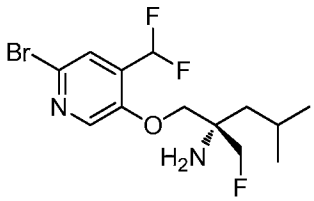
Prepared as previously described In Example 179 to afford (*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-6-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate (8.8 mg, 33%): ^{1}H NMR (500 MHz, DMSO-d6) δ 8.50 (s, 1H), 8.36 (d, *J* = 5.4 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 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 [(M+H)$^+$, calcd $C_{20}H_{26}F_3N_4O_3$, 427.2]; LC/MS retention time (method B): t_R = 1.62 min.

Example 181

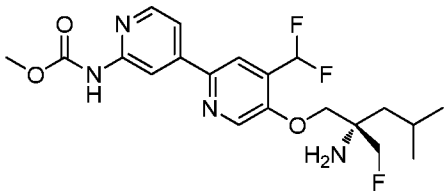
(*S*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





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: ^{1}H 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 [(M+H)$^+$, calcd $C_{13}H_{19}BrF_3N_2O$, 355.1]; LC/MS retention time (method B): t_R = 1.78 min.

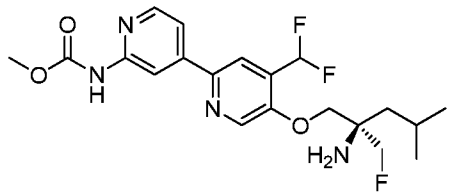


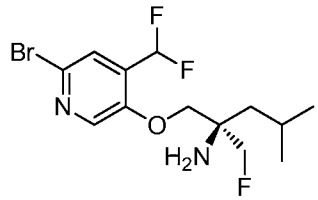
Part B: (S)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

Prepared as previously described for Example 179 to afford the titled product (4.0 mg, 17%): ^{1}H 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 $C_{20}H_{26}F_3N_4O_3$, 427.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 182

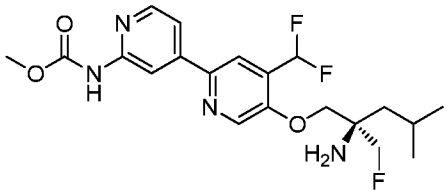
(*R*)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate





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: ^{1}H NMR (400 MHz, Methanol-d$_4$) 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); ^{19}F NMR (376 MHz, Chloroform-d) δ -119.62 , -226.06; LCMS (ESI) *m/e* 355.1 [(M+H)$^+$, calcd $C_{13}H_{19}BrF_3N_2O$, 355.1]; LC/MS retention time (method B): t_R = 1.79 min.

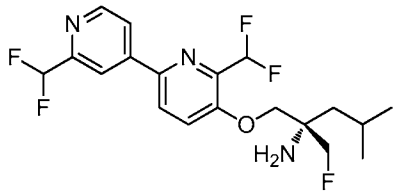


Part B: (R)-methyl (5-((2-amino-2-(fluoromethyl)-4-methylpentyl)oxy)-4-(difluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

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%): ^{1}H 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), 4.43 - 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 $C_{20}H_{26}F_3N_4O_3$, 427.2]; LC/MS retention time (method B): t_R = 1.65 min.

Example 183

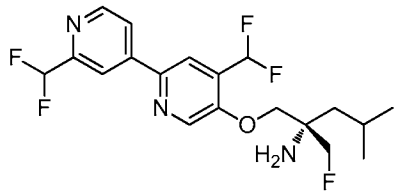
(*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



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%): ^{1}H 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), 7.88 (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 $C_{19}H_{23}F_5N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.90 min.

Example 184

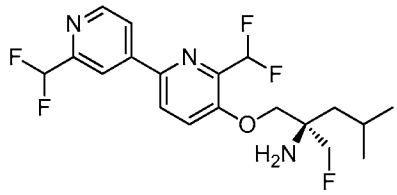
(*S*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



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%): ^{1}H 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 $C_{19}H_{23}F_5N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.86 min.

Example 185

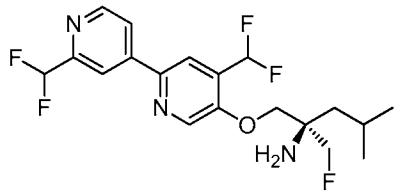
(*R*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



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%): ^{1}H 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 $C_{19}H_{23}F_5N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.87 min.

Example 186

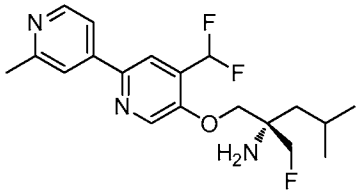
(*R*)-1-((2',4-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



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%): ^{1}H 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 $C_{19}H_{23}F_5N_3O$, 404.2]; LC/MS retention time (method B): t_R = 1.87 min.

Example 187

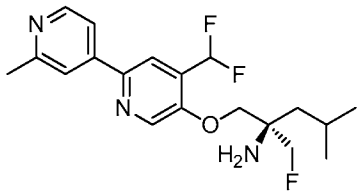
(*S*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine



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%): ^{1}H 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 $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.39 min.

Example 188

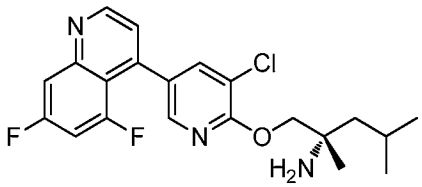
(*R*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine

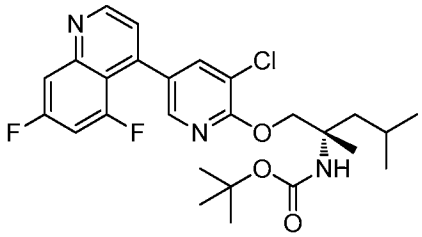


Prepared as previously described for Example 179 to afford (*R*)-1-((4-(difluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2-(fluoromethyl)-4-methylpentan-2-amine (20.5 mg, 59%): ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.71 (s, 1H), 8.54 (d, *J* = 5.4 Hz, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 5.2 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 $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.47 min.

Example 189

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

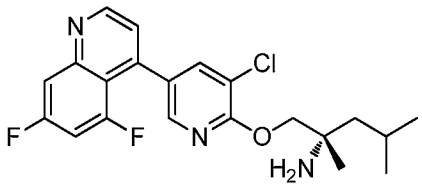




Part A: (S)-tert-butyl (1-((3-chloro-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Prepared as described in Example 179. 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 $C_{26}H_{31}F_2N_3Cl_1O_3$, 506.2]; LC/MS retention time (method B): t_R = 2.48 min.

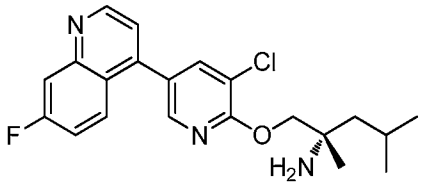


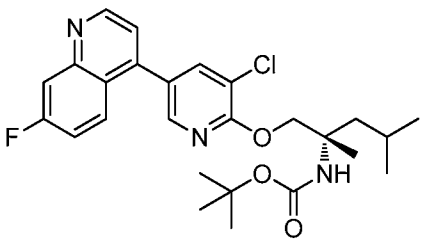
Part B: (S)-N-(4-(4-((2-amino-4-methylpentyl)oxy)-3-fluorophenyl)pyridin-2-yl)acetamide

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. ^{1}H 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* 406.0 [$(M+H)^+$, calcd $C_{21}H_{23}F_2N_3Cl_1O_1$, 406.1]; LC/MS retention time (method B): t_R = 2.03 min.

Example 190

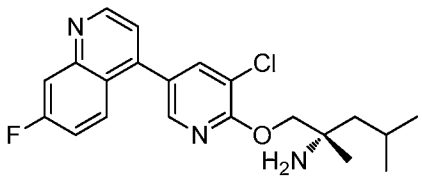
(*S*)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





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 131, Part A. Suzuki coupling was performed as described in Example 131, 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). ^{1}H 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 [(M+H)$^+$, calcd $C_{26}H_{32}F_1N_3Cl_1O_3$, 488.2]; LC/MS retention time (method B): t_R = 2.39 min.

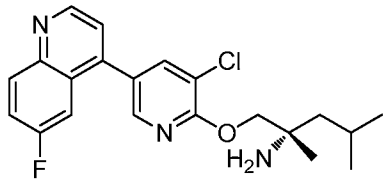


Part B: (S)-1-((3-chloro-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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 [(M+Na)$^+$, calcd $C_{21}H_{23}F_1N_3Cl_1O_1Na_1$, 410.1]; LC/MS retention time (method B): t_R = 1.85 min.

Example 191

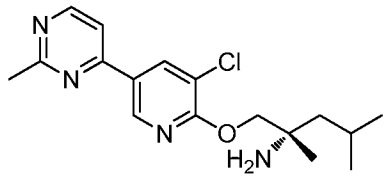
(*S*)-1-((3-chloro-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 190 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. ^{1}H 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

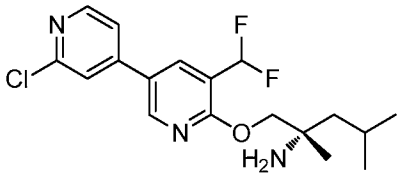
(*S*)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

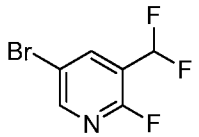


Prepared as in Example 59 to obtain (*S*)-1-((3-chloro-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine 10.1 mg, 0.030 mmol, 51% yield in two steps). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.94 (d, *J*=2.2 Hz, 1H), 8.76 (d, *J*=5.5 Hz, 1H), 8.63 (d, *J*=1.8 Hz, 1H), 7.95 (d, *J*=5.5 Hz, 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 [$(M-NH_2)^+$, calcd $C_{17}H_{21}N_3ClO$, 318.1]; LC/MS retention time (method B): t_R = 1.83 min.

Example 193

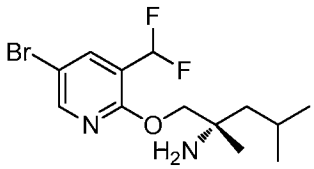
(*S*)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: 5-Bromo-3-(difluoromethyl)-2-fluoropyridine

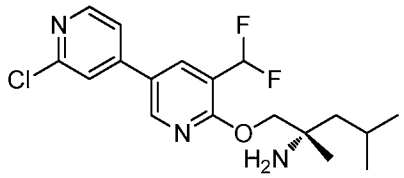
To a solution of 5-bromo-2-fluoronicotinaldehyde (0.8212 g, 4.03 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added DAST (1.064 mL, 8.05 mmol). The reaction was stirred at 0 °C for 1 h then warmed to room temperature. The stirring was continued for 3 h. The reaction was poured into an ice cold 1N NaOH solution. The organic layer was separated and the aqueous layer was extracted DCM (2x). The DCM layers were combined, dried (Na_2SO_4), 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. ^{1}H 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); ^{19}F NMR (376MHz, CHLOROFORM-d) δ -74.33 (br. s., 1F), -115.87 (s, 2F); LCMS (ESI) *m/e* 205.9 [(M-F)$^+$, calcd $C_6H_3BrNF_2$, 205.9]; LC/MS retention time (method B): t_R = 1.88 min.



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 (Na_2SO_4), filtered and concentrated

under reduced pressure. The product was purified by silica gel chromatography (eluted with 0- 10% methanol in CH_2Cl_2) 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. ^{1}H 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). ^{19}F NMR (376MHz, CHLOROFORM-d) δ -117.61 (s, 2F); LCMS (ESI) *m/e* 320.1 $[(M-NH_2)^+$, calcd $C_{13}H_{17}BrNF_2O$, 320.1]; LC/MS retention time (method B): t_R = 1.99 min.

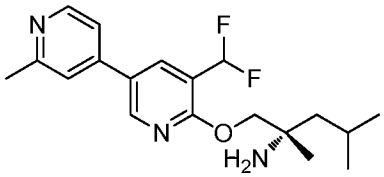


Part C: (S)-1-((2'-chloro-5-(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine

A mixture of 2N sodium carbonate solution (0.050 ml, 0.099 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichoromethane 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 diatomaceous earth (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. ^{1}H NMR (500MHz, DMSO-d_6) 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 $[(M-NH_2)^+$, calcd $C_{18}H_{20}N_2ClF_2O$, 353.1]; LC/MS retention time (method B): t_R = 1.96 min.

Example 194

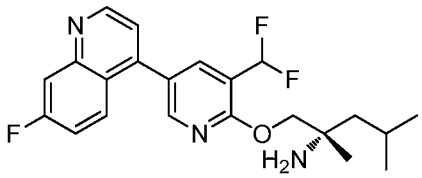
(*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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. ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method E): t_R = 2.62 min.

Example 195

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

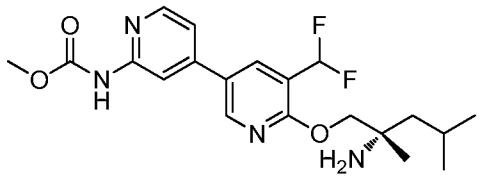


Part A: (S)-1-((3-(difluoromethyl)-5-(7-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Intermediate 7-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline was prepared as described in Example 131, Part A. 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). ^{1}H NMR (500MHz, DMSO-d$_6$) 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-NH$_2$)$^+$, calcd $C_{22}H_{22}N_2F_3O$, 387.2]; LC/MS retention time (method B): t_R = 1.86 min.

Example 196

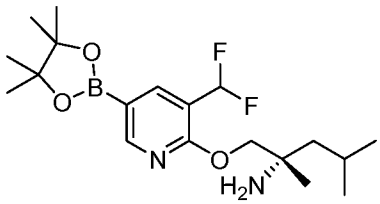
(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate



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). ^{1}H 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 $C_{20}H_{26}N_4F_2O_3Na$, 431.2]; LC/MS retention time (method B): t_R = 1.78 min.

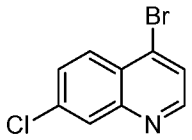
Example 197

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



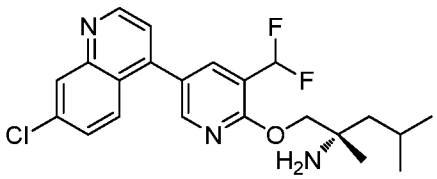
Part A: (S)-1-((3-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

A mixture of potassium acetate (0.018 g, 0.181 mmol), (*S*)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0204 g, 0.060 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.023 g, 0.091 mmol) in 1,4-dioxane (0.55 mL) was purged with nitrogen for 10 min. PdCl2(dppf) (1.328 mg, 1.815 µmol) was added to the reaction mixture then the reaction was heated at 80 °C for 2 h. The crude reaction mixture was concentrated under reduced pressure and carried forward as is.



Part B: 4-bromo-7-chloroquinoline

To a 20 mL microwave tube was added 4,7-dichloroquinoline (0.3315 g, 1.674 mmol) and propionitrile (3 mL), followed by TMS-Br (0.434 mL, 3.35 mmol) at room temperature. A precipitate formed. The tube was sealed and heated to 100 °C for 12 h. The reaction was cooled to room temperature. The crude mixture was poured into ice-cooled NaOH (1N, 3 mL) and the tube was rinsed with water. The aqueous layer was extracted with diethyl ether (3x5 mL). The diethyl ether layer were combined, dried (Na2SO4), filtered and concentrated under reduced pressure to give the 4-bromo-7-chloroquinoline (300 mg, 1.126 mmol, 67% yield) as a yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.70 (d, *J*=4.6 Hz, 1H), 8.17 (d, *J*=8.8 Hz, 1H), 8.14 (d, *J*=2.0 Hz, 1H), 7.73 (d, *J*=4.6 Hz, 1H), 7.63 (dd, *J*=9.0, 2.0 Hz, 1H); LCMS (ESI) *m/e* 241.9 [(M+H)$^+$, calcd C_9H_5BrClN, 241.9].

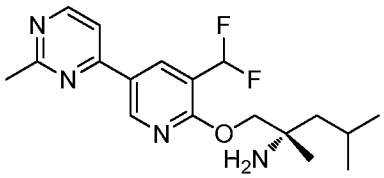


Part C: (*S*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Suzuki coupling between 4-bromo-7-chloroquinoline (13.34 mg, 0.055 mmol) and (*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 (21.13 mg, 0.055 mmol) 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). ^{1}H 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 $C_{22}H_{24}ClN_3F_2ONa$, 442.2]; LC/MS retention time (method B): t_R = 2.09 min.

Example 198

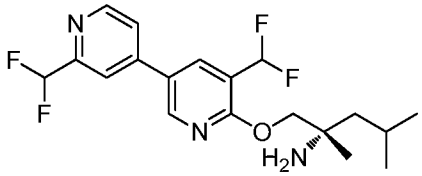
(*S*)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



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 197, Part A. 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). ^{1}H 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-NH$_2$)$^+$, calcd $C_{18}H_{22}N_3F_2O$, 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

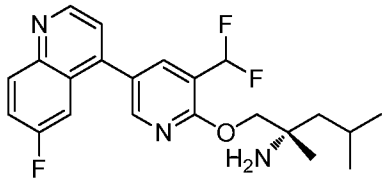


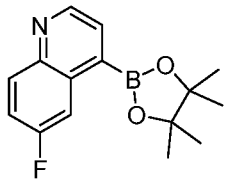
Intermediate (*S*)-1-((3-(difluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine was prepared as described in Example 197, Part A. Suzuki reaction was performed as described in Example 193. Obtained (*S*)-1-((2',5-bis(difluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine (9.2 mg, 0.023 mmol, 39% yield). ^{1}H 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-NH_2)$^+$, calcd $C_{19}H_{21}N_2F_4O$, 369.2]; LC/MS retention time (method B): t_R = 1.91 min.

Example 200

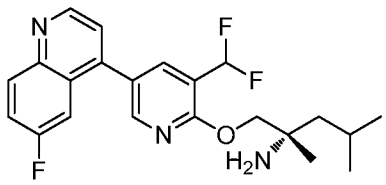
(*S*)-1-((3-(difluoromethyl)-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

A mixture of potassium acetate (0.060 g, 0.610 mmol), 4-bromo-7-fluoroquinoline (0.046 g, 0.203 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.062 g, 0.244 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen for 10 min. PdCl2(dppf) (4.47 mg, 6.10 µmol) was added and the reaction was heated at 80 °C for 5 hours. The reaction was cooled to room temperature and was carried forward as it is assuming quantitative yield).



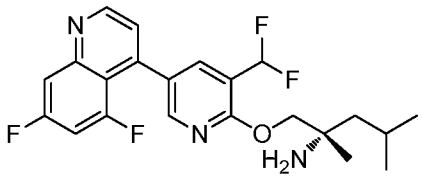
Part B: (S)-1-((3-(difluoromethyl)-5-(6-fluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

A mixture of sodium carbonate (0.171 ml, 0.342 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (6.98 mg, 8.55 µmol), (*S*)-1-((5-bromo-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-

dimethylpentan-2-amine (0.0272 g, 0.081 mmol) and 6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.047 g, 0.171 mmol) in 1,4-dioxane (0.8 ml) (degassed) was heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature and filtered through celite. The filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (XBridge C18 column, mobile phase: acetonitrile, water, 10-mM ammonium acetate) to afford (*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). ^{1}H 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.

Example 201

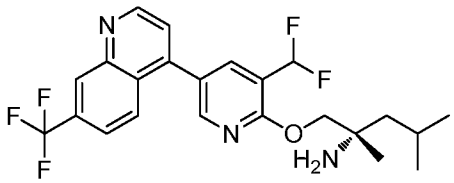
(*S*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



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). ^{1}H 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.

Example 202

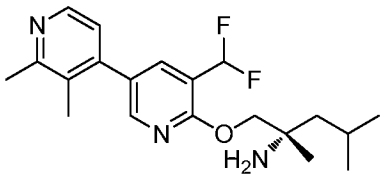
(*S*)-1-((3-(difluoromethyl)-5-(7-(trifluoromethyl)quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared 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). ^{1}H NMR (500MHz, 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 $C_{23}H_{22}N_2F_5O$, 437.2]; LC/MS retention time (method B): t_R = 2.13 min.

Example 203

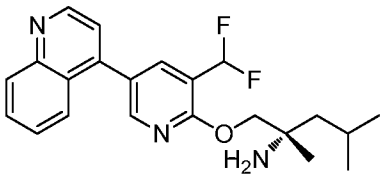
(*S*)-1-((5-(difluoromethyl)-2',3'-dimethyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared 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). ^{1}H 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 $C_{20}H_{25}N_2F_2O$, 347.2]; LC/MS retention time (method B): t_R = 1.48 min.

Example 204

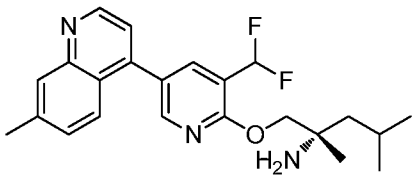
(*S*)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



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). ^{1}H 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); 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-dimethylpentan-2-amine

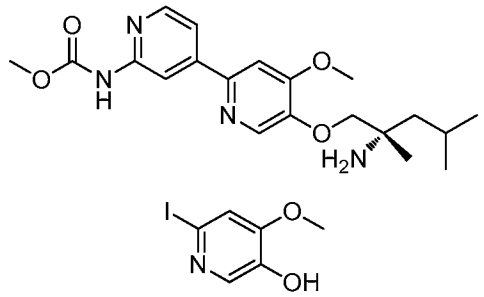


A mixture of 2N sodium carbonate solution (0.146 mL, 0.291 mmol), (*S*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.0611 g, 0.146 mmol) (Example 197) ,2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.018 g, 0.146 mmol) and 1,1'- bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichoromethane complex (5.94 mg, 7.28 µmol) 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 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). ^{1}H 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), 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.

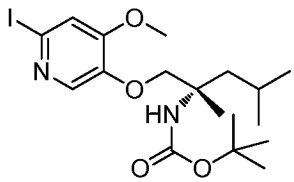
Example 206

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



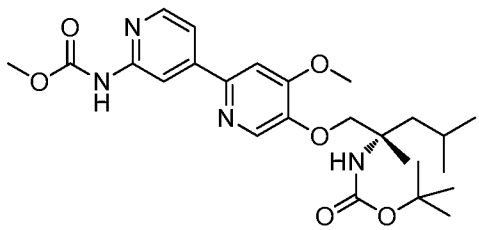
Part A: 6-Iodo-4-methoxypyridin-3-ol

n- BuLi (0.319 mL, 0.797 mmol) was added to the THF (4 mL) solution of 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 NH_4Cl (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 water. The ethyl acetate layer was separated, dried (Na_2SO_4), 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). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.95 (s, 1H), 7.14 (s, 1H), 3.92 (s, 3H), one exchangeable proton was not observed; LCMS (ESI) *m/e* 251.9 [$(M+H)^+$, calcd $C_6H_7INO_2$, 252.0]; LC/MS retention time (method B): t_R = 0.85 min.



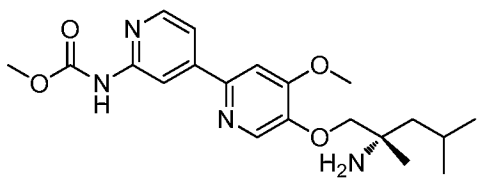
Part B: (S)-tert-butyl (1-((6-iodo-4-methoxypyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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 µmol, 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.



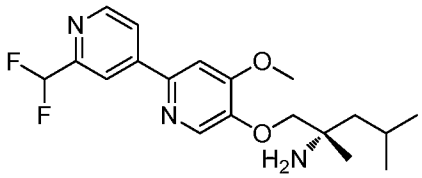
Part D: (S)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate

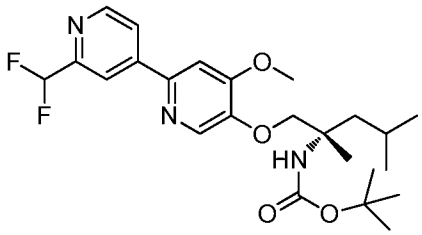
TFA deprotection was performed as described in Example 32. Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-methoxy-[2,4'-bipyridin]-2'-yl)carbamate (1.2 mg, 3.09 µmol, 66% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (s, 1H), 8.34 (d, *J*=5.1 Hz, 1H), 8.31 (s, 1H), 7.69 (d, *J*=5.1 Hz, 1H), 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

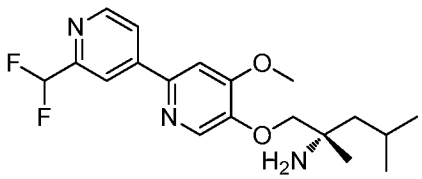
(*S*)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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*)-*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 $C_{24}H_{34}F_2N_3O_4$, 466.2]; LC/MS retention time (method B): t_R = 2.65 min.

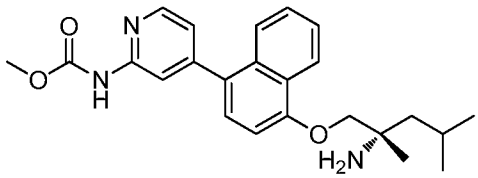


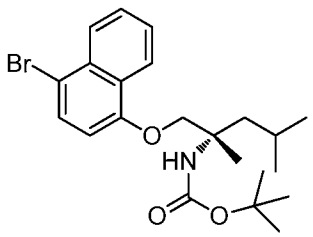
Part B: (S)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

TFA deprotection was performed as described in Example 32. Obtained (*S*)-1-((2'-(difluoromethyl)-4-methoxy-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (5.0 mg, 0.014 mmol, 53% yield). ^{1}H 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.

Example 208

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

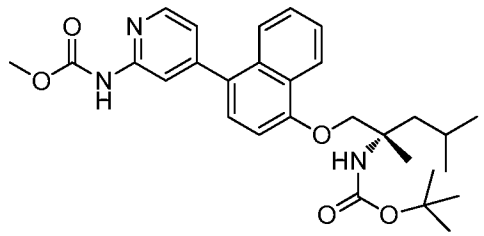




Part A: (S)-tert-butyl (1-((4-bromonaphthalen-1-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

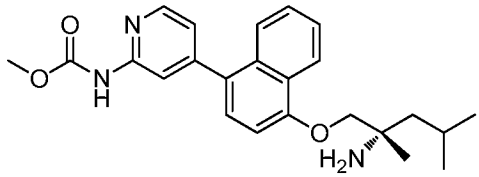
A mixture of potassium carbonate (0.124 g, 0.897 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.132 g, 0.448 mmol) and 4-bromonaphthalen-1-ol (0.1 g, 0.448 mmol) in DMF (1 mL) was heated at 80 °C for overnight. The reaction was diluted with ethyl acetate and washed with NaOH (1N) one time, followed by water two times. The ethyl acetate layer was separated, dried (Na2SO4), filtered and concentrated. The residue was purified by silica gel chromatography (0 to 5% ethyl acetate in hexane) to afford (*S*)-*tert*-butyl (1-((4-bromonaphthalen-1-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (37 mg, 0.085 mmol, 19% yield) as a yellow oil. ^{1}H 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.



Part B: Boc protected (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

A mixture of sodium carbonate (0.034 ml, 0.069 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (1.965 mg, 2.406 µmol), (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic acid (0.013 g, 0.069 mmol) and (*S*)-*tert*-butyl (1-((4-bromonaphthalen-1-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.015 g, 0.034 mmol) in 1,4-dioxane (0.3 mL) (degassed) was heated at 80 °C for 2 h. The reaction mixture 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 silica gel chromatography (0 to 25% ethyl acetate in hexane) to afford 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). ^{1}H 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 $C_{29}H_{38}N_3O_5$, 508.3]; LC/MS retention time (method B): t_R = 2.30 min.

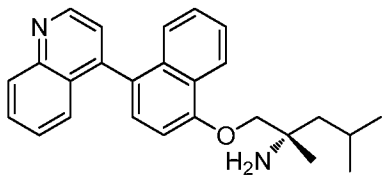


Part C: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)naphthalen-1-yl)pyridin-2-yl)carbamate

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). ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{24}H_{30}N_3O_3$, 408.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 209

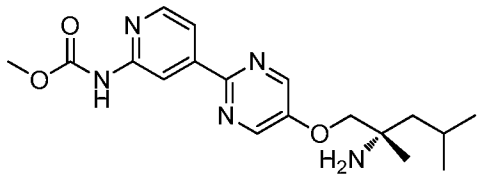
(*S*)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine

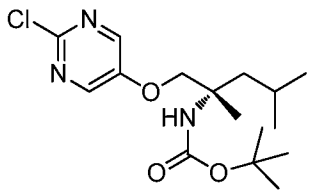


Prepared as described in Example 208. Obtained (*S*)-2,4-dimethyl-1-((4-(quinolin-4-yl)naphthalen-1-yl)oxy)pentan-2-amine (6.3 mg, 0.016 mmol, 98% yield). ^{1}H NMR (500MHz, DMSO-d$_6$) δ 9.03 (d, *J*=4.4 Hz, 1H), 8.44 (d, *J*=6.2 Hz, 1H), 8.15 (d, *J*=8.4 Hz, 1H), 7.78 (t, *J*=7.5 Hz, 1H), 7.58 (t, *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 exchangeable protons not observed; LCMS (ESI) *m/e* 385.2 [(M+H)$^+$, calcd $C_{26}H_{29}N_2O$, 385.2]; LC/MS retention time (method B): t_R = 1.70 min.

Example 210

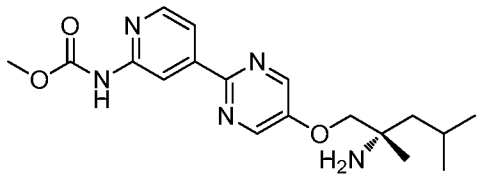
(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate





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). ^{1}H 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).



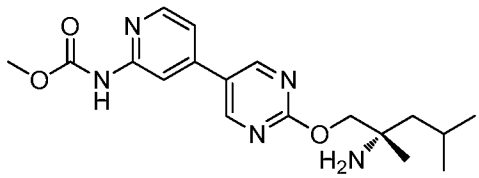
Part B: (S)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-2-yl)pyridin-2-yl)carbamate

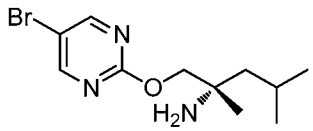
A mixture of 2N sodium carbonate solution (0.073 mL, 0.145 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (2.97 mg, 3.64 μmol) , (*S*)-*tert*-butyl (1-((2-chloropyrimidin-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate and (2-((methoxycarbonyl)amino)pyridin-4-yl)boronic 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 (Na_2SO_4), 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). ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{18}H_{26}N_5O_3$, 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

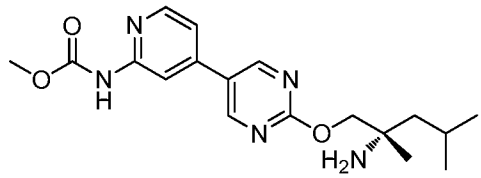




Part A: (S)-1-((5-bromopyrimidin-2-yl)oxy)-2,4-dimethylpentan-2-amine

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 (Na_2SO_4), 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-bromopyrimidin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.014 g, 0.050 mmol, 25% yield). ^{1}H 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 $C_{11}H_{18}BrN_3ONa$, 310.1]; LC/MS retention time (method B): t_R = 1.67 min.

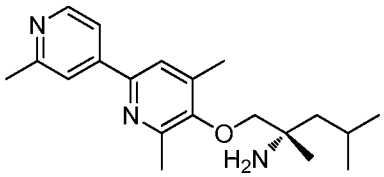


Part B: (S)-methyl (4-(2-((2-amino-2,4-dimethylpentyl)oxy)pyrimidin-5-yl)pyridin-2-yl)carbamate

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). ^{1}H 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 $C_{18}H_{26}N_5O_3$, 360.2]; LC/MS retention time (method B): t_R = 1.76 min.

Example 212

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

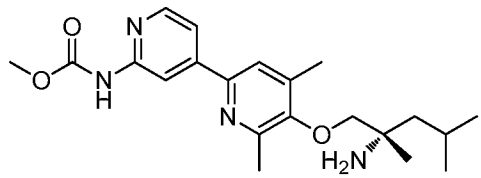


Suzuki reaction was performed as described in Example 193. Obtained (*S*)-2,4-dimethyl-1-((2',4,6-trimethyl-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine (10.3 mg, 0.031 mmol, 57% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.57 (d, *J*=5.3 Hz, 1H), 7.75 (s, 1H), 7.62 (dd, *J*=5.1, 1.4 Hz, 1H), 7.46 (s, 1H), 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.

Example 213

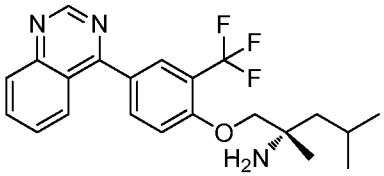
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4,6-dimethyl-[2,4'-bipyridin]-2'-yl)carbamate



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). ^{1}H 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 (dquin, *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.

Example 214

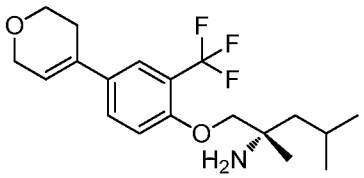
(*S*)-2,4-dimethyl-1-(4-(quinazolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

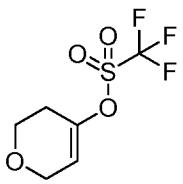


Prepared as described in Example 19. Obtained (*S*)-2,4-dimethyl-1-(4-(quinazolin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (8.5 mg, 0.020 mmol, 19% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.17 - 8.03 (m, 5H), 7.79 (t, *J*=7.5 Hz, 1H), 7.47 (d, *J*=8.4 Hz, 1H), 3.94 (d, *J*=7.3 Hz, 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.

Example 215

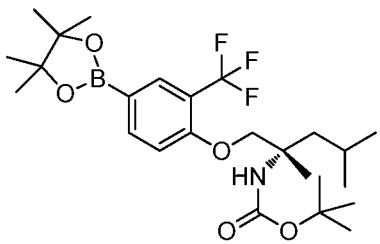
(*S*)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine





Part A: 3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonate

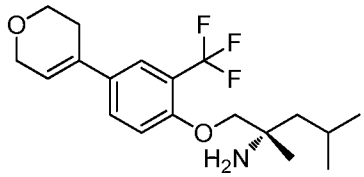
KHMDS (6.66 mL, 3.33 mmol) was added to the THF (7 mL) solution of dihydro-2*H*-pyran-4(3*H*)-one (0.2224 g, 2.221 mmol) and 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (0.952 g, 2.67 mmol) at -78 °C. The reaction was stirred for 30 min. The reaction was diluted with diethyl ether and washed with water (3x). The diethyl ether layer was separated, dried (Na_2SO_4), filtered and concentrated. The crude material was carried on without further purification.



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

A solution of (*S*)-*tert*-butyl (1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (6.5 g, 14.31 mmol), bis(pinacolato)diboron (7.27 g, 28.6 mmol), potassium acetate (4.21 g, 42.9 mmol) in 1,4-dioxane (100 mL) was purged with argon for 5min. $PdCl_2$ (dppf)-CH_2Cl_2 adduct (1.168 g, 1.431 mmol) was

added to the reaction mixture under argon and was heated at 84 °C for 14 h. The reaction mixture was filtered through celite and the celite bed was washed with ethyl acetate (200 mL). The organic layer was washed with water (100 mL). The aqueous layer was re-extracted with ethyl acetate (2X100 mL). The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated which afforded crude (*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. The crude product was dissolved in 50 mL of DCM, adsorbed on silica gel (60-120), purified silica gel chromatography (0-15% of ethyl acetate/hexane) to give (*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 (6.01 g, 11.99 mmol, 84% yield) as a off-white semi-solid. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.87-7.90 (m, 1H), 7.80 (s, 1H), 7.21 (d, *J* = 8.40 Hz, 1H), 6.53 (s, 1H), 4.07-4.25 (m, 2H), 1.70-1.79 (m, 2H), 1.45-1.50 (m, 1H), 1.26-1.35 (m, 9H), 1.08-1.20 (m, 12H), 0.82-0.91 (m, 6H) ppm.



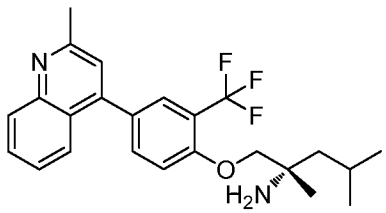
Part C: (S)-1-(4-(3,6-dihydro-2H-pyran-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

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 µmol), 3,6-dihydro-2*H*-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 (Na_2SO_4), 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-2*H*-pyran-4-yl)-2-

(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (2.7 mg, 0.213 mmol, 7% yield over three steps). ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{19}H_{27}F_3NO_2$, 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

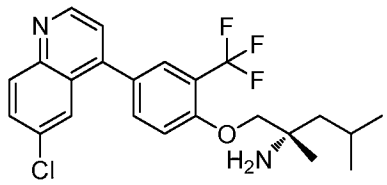


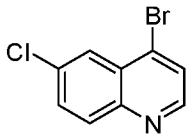
A mixture of 2N sodium carbonate solution (0.157 mL, 0.314 mmol), 1,1'-bis(diphenylphosphine)ferrocene-palladium(II)dichloride dichloromethane complex (8.97 mg, 10.99 µmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (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 (Na_2SO_4), 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). ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{24}H_{28}F_3N_2O$, 417.2]; LC/MS retention time (method B): t_R = 2.26 min.

Example 217

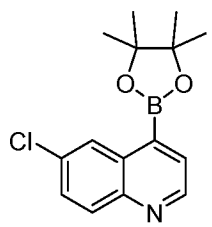
(*S*)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine





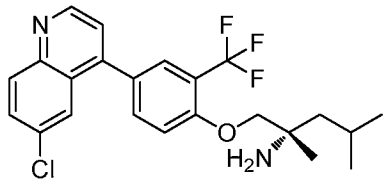
Part A: 4-bromo-6-chloroquinoline

To a 20 mL microwave tube was added 4,7-dichloroquinoline (0.3315 g, 1.674 mmol) and propionitrile (3 mL), followed by TMS-Br (0.434 ml, 3.35 mmol) at room temperature. A precipitate was formed. The tube was sealed and heated to 100 °C for 16 h. The reaction mixture was cooled to room temperature then poured into ice-cooled NaOH (1N, 3 mL) and the tube was rinsed with water. The aqueous layer was extracted with diethyl ether (3x5 mL). The diethyl ether layers were combined, dried (Na2SO4), filtered and concentrated to give the crude product as a yellow solid. The material was purified by silica gel chromatography (EtOAc in hexanes to afford 4-bromo-6-chloroquinoline (300 mg, 1.126 mmol, 67% yield) as a plae yellow solid. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.70 (d, *J*=4.6 Hz, 1H), 8.17 (d, *J*=8.8 Hz, 1H), 8.14 (d, *J*=2.0 Hz, 1H), 7.73 (d, *J*=4.6 Hz, 1H), 7.63 (dd, *J*=9.0, 2.0 Hz, 1H).



Part B: 6-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

A mixture of potassium acetate (0.136 g, 1.382 mmol), 4-bromo-7-chloroquinoline (0.1117 g, 0.461 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.140 g, 0.553 mmol) in 1,4-dioxane (0.5 mL) was purged with nitrogen for 10 min. PdCl2(dppf) (10.11 mg, 0.014 mmol) was added to the reaction mixture at room temperature and the reaction was heated at 80 °C for 5 h. The reaction was cooled to room temperature and carried forward without purification assuming quantitative yield. LCMS (ESI) *m/e* 290.1 [$(M+H)^+$, calcd $C_{15}H_{18}BClNO_2$, 290.1]; LC/MS retention time (method B): t_R = 1.17 min.

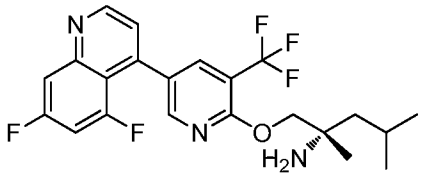


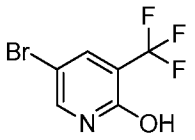
Part C: (*S*)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

Preparation was described as Example 19. Obtained (*S*)-1-(4-(6-chloroquinolin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (3.9 mg, 8.66 µmol, 7% yield). ^{1}H NMR (500MHz, DMSO-d_6) 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

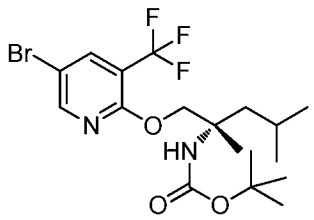
(*S*)-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: 5-Bromo-3-(trifluoromethyl)pyridin-2-ol

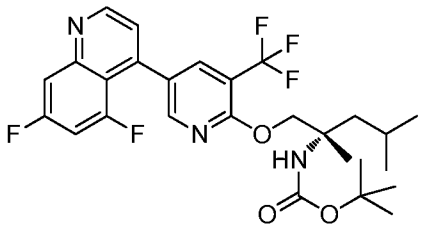
NBS (2.334 g, 13.11 mmol) was added portionwise to a solution of 3-(trifluoromethyl)pyridin-2-ol (1.6449 g, 10.09 mmol) in THF (15 mL) at room temperature. The reaction was stirred at room temperature over the weekend. The reaction was diluted with ethyl acetate and washed with water three times. The 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.



Part B: (S)-tert-butyl (1-((5-bromo-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

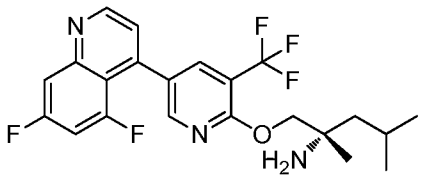
A mixture of potassium carbonate (0.113 g, 0.814 mmol), (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.1593 g, 0.543 mmol) and 5-bromo-3-(trifluoromethyl)pyridin-2-ol (0.197 g, 0.814 mmol) in DMF (2 mL) was heated at 80 °C overnight. The reaction was diluted with ethyl acetate and washed with water three times. The ethyl acetate layer was separated, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was 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). ^{1}H 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, 1H), 1.39 (s, 9H), 1.37 (s, 3H), 0.97 (m, 6H); ^{19}F NMR (376MHz, CHLOROFORM-

d) δ -64.11 (s, 3F). LCMS (ESI) *m/e* 476.9 [(M+Na)$^+$, calcd $C_{18}H_{26}BrF_3N_2O_3Na$, 477.1]; LC/MS retention time (method B): t_R = 2.54 min.



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)$^+$, calcd $C_{27}H_{31}F_5N_3O_3$, 540.2]; LC/MS retention time (method B): t_R = 2.53 min.

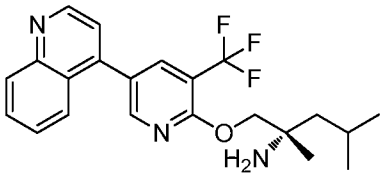


Part D: (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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 [(M+H)$^+$, calcd $C_{22}H_{23}F_5N_3O$, 440.2]; LC/MS retention time (method B): t_R = 2.04 min.

Example 219

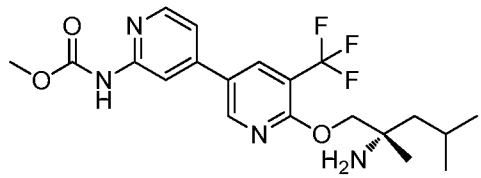
(*S*)-2,4-dimethyl-1-((5-(quinolin-4-yl)-3-(trifluoromethyl)pyridin-2-yl)oxy)pentan-2-amine



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. ^{1}H 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 [(M+H)$^+$, calcd $C_{22}H_{25}F_3N_3O$, 404.4]; LC/MS retention time (method B): t_R = 1.77 min.

Example 220

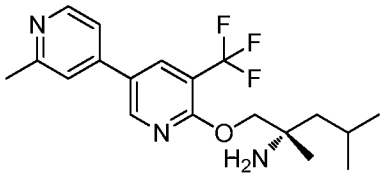
(*S*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(trifluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate



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. ^{1}H 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, 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.

Example 221

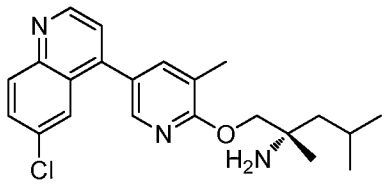
(*S*)-2,4-dimethyl-1-((2'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)pentan-2-amine

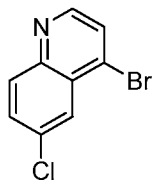


Prepared as described in Example 218. Obtained (*S*)-2,4-dimethyl-1-((2'-methyl-5-(trifluoromethyl)-[3,4'-bipyridin]-6-yl)oxy)pentan-2-amine (4.6 mg, 0.012 mmol, 68% yield). ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.87 (s, 1H), 8.52 (d, *J*=5.1 Hz, 1H), 8.46 (s, 1H), 7.72 (s, 1H), 7.62 (d, *J*=4.0 Hz, 1H), 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 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

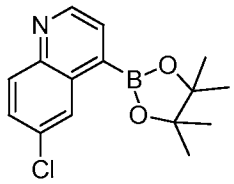




Part A: 4-Bromo-6-chloroquinoline

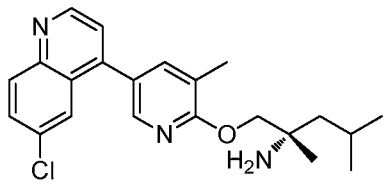
To a 20 mL microwave tube was added 4,6-dichloroquinoline (0.3446 g, 1.740 mmol) and propionitrile (1ml), followed by TMS-Br (0.451 ml, 3.48 mmol) at room temperature. A precipitate was formed. The tube was sealed and heated to 100°C for overnight. The reaction was cooled to room temperature. The crude was poured into iced NaOH(1N, 3 mL) solution and the tube was washed with water. The aqueous was extracted three times with diethyl ether. The diethyl ether layer was combined, dried (Na2SO4), filtered and concentrated to give 4-bromo-6-

chloroquinoline (0.322 g, 1.33 mmol, 76% yield) as a yellow solid. ^{1}H 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 C_9H_5BrNCl,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

A mixture of potassium acetate (0.136 g, 1.382 mmol), 4-bromo-7-chloroquinoline (0.1117 g, 0.461 mmol), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.140 g, 0.553 mmol) in 1,4-dioxane (0.5 mL) was purged with nitrogen for 10 min. PdCl2(dppf) (10.11 mg, 0.014 mmol) was added and the reaction was heated at 80 °C for 5 h. The reaction was cooled to room temperature and was carried on without further purification assuming quantitative yield. LCMS (ESI) *m/e* 207.9 [$(M-NH_2)^+$, calcd $C_9H_7BNClO_2$, 207.0]; LC/MS retention time (method B): t_R = 1.21 min.



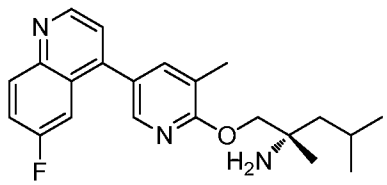
Part C: (S)-1-((5-(6-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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-NH_2)$^+$, calcd $C_{22}H_{24}N_2ClO$, 367.2]; LC/MS retention time (method B): t_R = 1.88 min.

Example 223

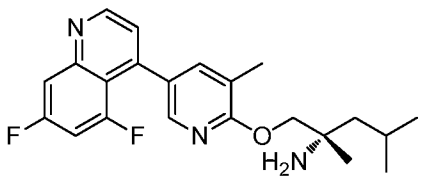
(*S*)-1-((5-(6-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

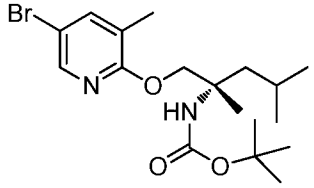


Prepared as described in Example 193. Obtained (*S*)-1-((5-(6-fluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (9.7 mg, 0.026 mmol, 14% yield). ^{1}H NMR (400MHz, CHLOROFORM-d) δ 8.92 (d, *J*=4.5 Hz, 1H), 8.31 - 8.16 (m, 1H), 8.12 (d, *J*=2.0 Hz, 1H), 7.61 - 7.49 (m, 3H), 7.34 (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 $C_{22}H_{27}N_3FO$, 368.2]; LC/MS retention time (method B): t_R = 1.78 min.

Example 224

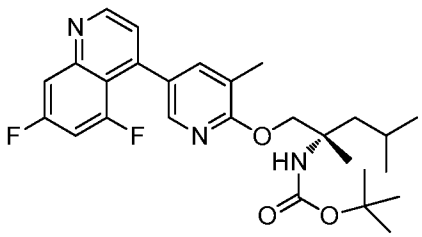
(*S*)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





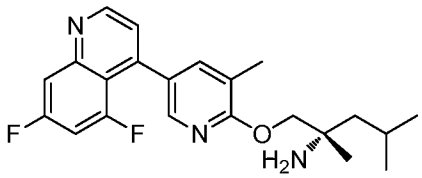
Part A: (S)-tert-butyl (1-((5-bromo-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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 $C_{18}H_{29}BrN_2O_3Na$, 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 $C_{27}H_{34}N_3F_2O_3$, 486.3]; LC/MS retention time (method B): t_R = 2.44 min.



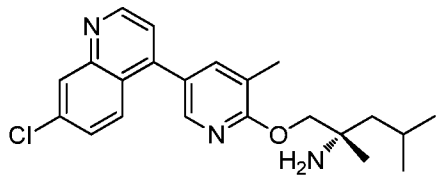
Part C: (S)-1-((5-(5,7-difluoroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H NMR (500MHz, DMSO-d_6) 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

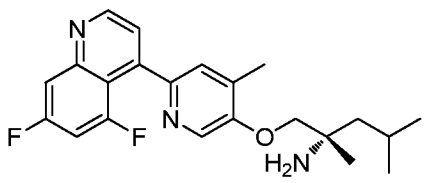
(*S*)-1-((5-(7-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

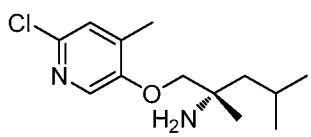


Prepared as described in Example 193. Obtained (*S*)-1-((5-(7-chloroquinolin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (22.5 mg, 0.058 mmol, 51% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.98 (d, *J*=4.4 Hz, 1H), 8.17 (s, 2H), 7.96 - 7.91 (m, 1H), 7.81 (s, 1H), 7.66 (dd, *J*=9.0, 2.0 Hz, 1H), 7.53 (d, *J*=4.4 Hz, 1H), 4.15 - 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.

Example 226

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

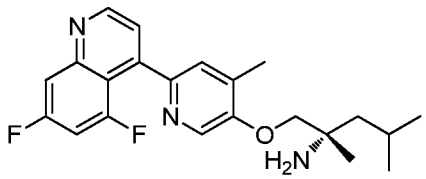




Part A: (S)-1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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 CH_2Cl_2 (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 $C13H_{22}ClN_2O$, 257.1]; LC/MS retention time (method B): t_R = 1.64 min.

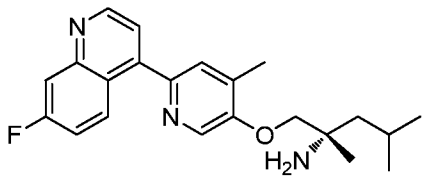


Part B: (S)-1-((6-(5,7-difluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

Suzuki coupling was performed as described in Example 193. 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). ^{1}H 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 $C_{22}H_{26}F_2N_3O$, 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

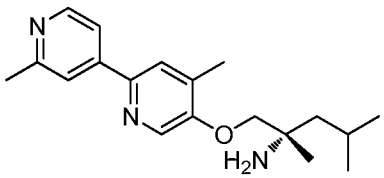


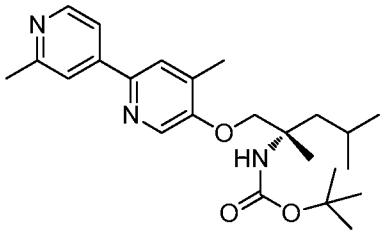
Prepared as described in Example 226. Obtained (*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (6.0 mg, 0.016 mmol, 63% yield). ^{1}H NMR (400MHz, DMSO-d_6) δ 8.98 (d, *J*=4.5 Hz, 1H), 8.47 (s, 1H), 8.34 (dd, *J*=9.3, 6.3 Hz, 1H), 7.82 (dd, *J*=10.3, 2.8 Hz, 1H), 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 $C_{22}H_{27}FN_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 228

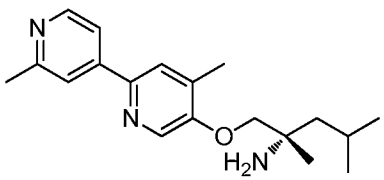
(*S*)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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

Suzuki coupling was performed as described in Example 193. The crude was used in the next reaction without purification. LCMS (ESI) *m/e* 414.0 $[(M+H)^+$, calcd $C_{24}H_{36}N_3O_3$, 414.3]; LC/MS retention time (method B): t_R = 2.02 min.



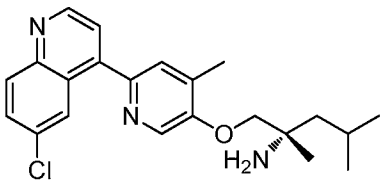
Part B: (S)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

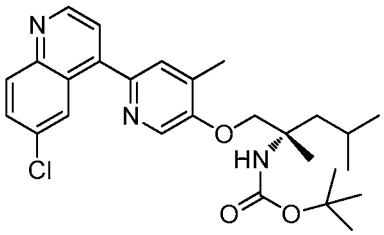
TFA deprotection as described in Example 32. Obtained (*S*)-1-((2',4-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (2.2 mg, 6.95 µmol, 17% yield over two steps). ^{1}H NMR (600MHz, DMSO-d_6) δ 8.50 (d, *J*=5.1 Hz, 1H), 8.34 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.78 (d, *J*=5.1 Hz, 1H), 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

[$(M+H)^+$, calcd $C_{19}H_{28}N_3O$, 314.2]; LC/MS retention time (method B): t_R = 1.50 min.

Example 229

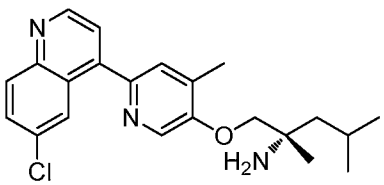
(*S*)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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

Suzuki coupling was performed as described in Example 193. The crude was used in the next reaction without purification. LCMS (ESI) *m/e* 483.9 [$(M+H)^+$, calcd $C_{27}H_{35}ClN_3O_3$, 484.2]; LC/MS retention time (method B): t_R = 2.24 min.



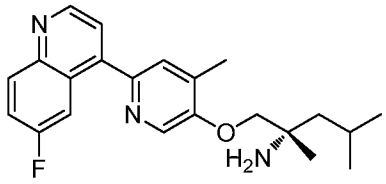
Part B: (S)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

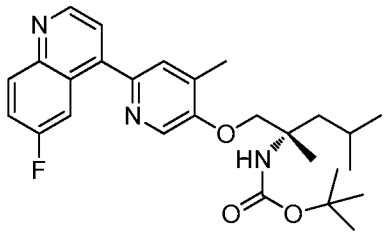
TFA deprotection as described in Example 32. Obtained (*S*)-1-((6-(6-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (6.8 mg, 0.017 mmol, 16% yield over two steps). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.00 (d, *J*=4.4 Hz, 1H), 8.48 (s, 1H), 8.40 (d, *J*=2.2 Hz, 1H), 8.12 (d, *J*=9.2 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 $C_{22}H_{27}ClN_3O$, 384.2]; LC/MS retention time (method B): t_R = 1.81 min.

Example 230

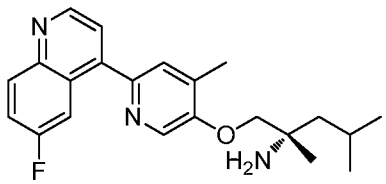
(*S*)-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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 $C_{27}H_{35}FN_3O_3$, 468.3]; LC/MS retention time (method B): t_R = 2.22 min.



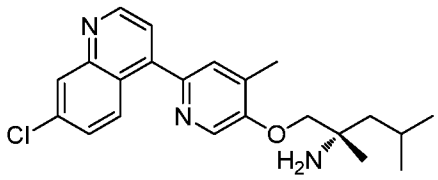
Part B: (S)-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

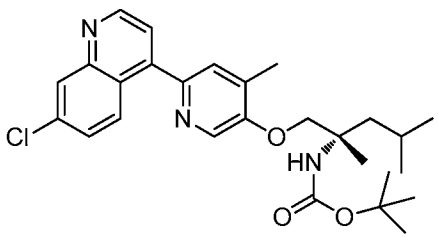
TFA deprotection as described in Example 32. Obtained (*S*)-1-((6-(6-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (21.7

mg, 0.058 mmol, 82% yield). ^{1}H 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 $C_{22}H_{27}FN_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 231

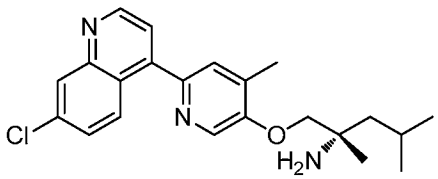
(*S*)-1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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.

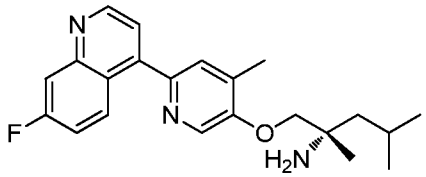


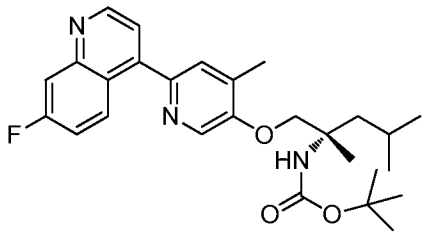
Part B: (S)-1-((6-(7-chloroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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.

Example 232

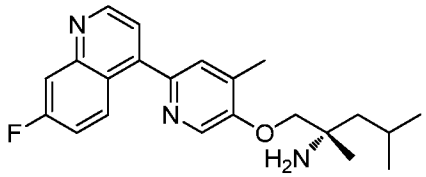
(*S*)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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 $C_{27}H_{35}FN_3O_3$, 468.3]; LC/MS retention time (method B): t_R = 2.24 min.

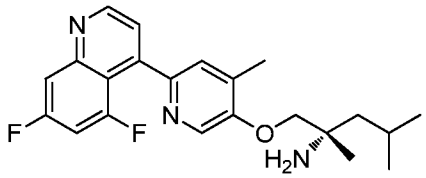


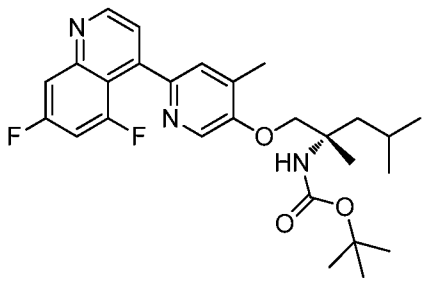
Part B: (S)-1-((6-(7-fluoroquinolin-4-yl)-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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 (m, 6H), two exchangeable protons not observed; LCMS (ESI) *m/e* 368.0 [$(M+H)^+$, calcd $C_{22}H_{27}FN_3O$, 368.2]; LC/MS retention time (method B): t_R = 1.67 min.

Example 233

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

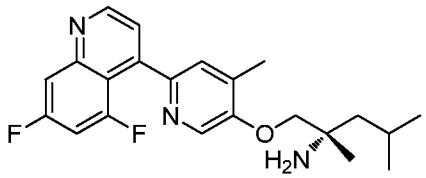




Part A: (S)-tert-butyl (1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

Suzuki coupling was performed as described in Example 193. 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.

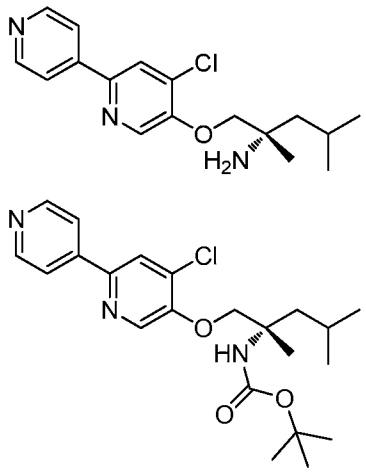


Part B: (S)-1-((4-chloro-6-(5,7-difluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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.

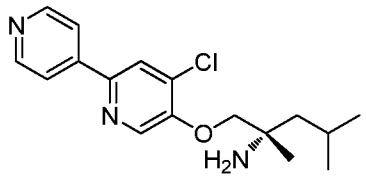
Example 234

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



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

Suzuki coupling was performed as described in Example 193. 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). ^{1}H 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 Hz, 1H), 1.44 (s, 3H), 1.40 (s, 9H), 1.01 (m, 6H). LCMS (ESI) *m/e* 420.2 [(M+H)$^+$, calcd $C_{22}H_{31}ClN_3O_3$, 420.2]; LC/MS retention time (method A): t_R = 2.07 min.

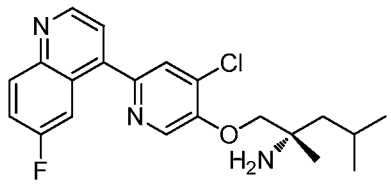


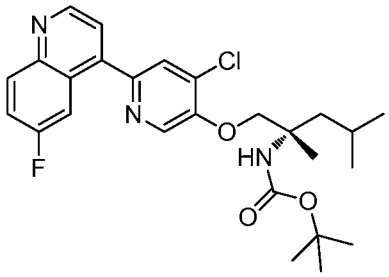
Part B: (S)-1-((4-chloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H NMR (500MHz, DMSO-d_6) 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.

Example 235

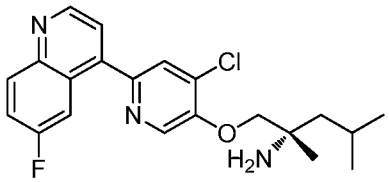
(*S*)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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.

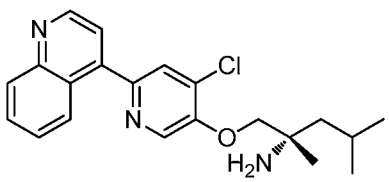


Part B: (S)-1-((4-chloro-6-(6-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{21}H_{24}ClFN_3O$, 388.2]; LC/MS retention time (method B): t_R = 1.75 min.

Example 236

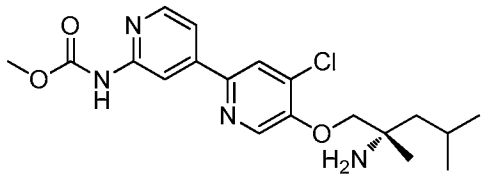
(*S*)-1-((4-chloro-6-(quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine



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 □mol, 16% yield). ^{1}H NMR (500MHz, DMSO-d$_6$) 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 $C_{21}H_{25}ClN_3O$, 370.2]; LC/MS retention time (method B): t_R = 1.75 min.

Example 237

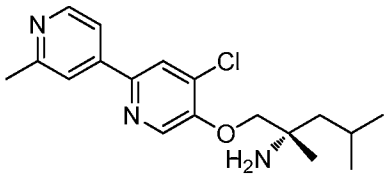
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-chloro-[2,4'-bipyridin]-2'-yl)carbamate

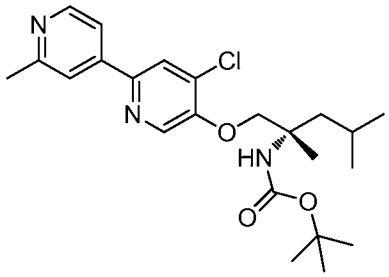


Suzuki coupling was performed as described in Example 193. Obtained (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-4-chloro-[2,4'-bipyridin]-2'-yl)carbamate (8.1 mg, 0.020 mmol, 35% yield). ^{1}H NMR (600MHz, DMSO-d$_6$) δ 8.59 (s, 1H), 8.52 (s, 1H), 8.34 (d, *J*=5.5 Hz, 1H), 8.19 (s, 1H), 7.67 (d, *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 $C_{19}H_{26}ClN_4O_3$, 393.2]; LC/MS retention time (method B): t_R = 1.63 min.

Example 238

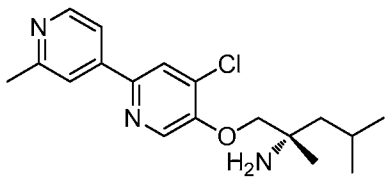
(*S*)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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). ^{1}H 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 $C_{23}H_{33}ClN_3O_3$, 433.2]; LC/MS retention time (method B): t_R = 2.07 min.

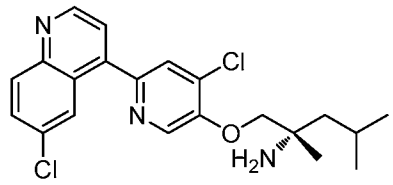


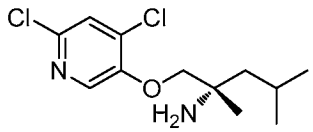
Part B: (S)-1-((4-chloro-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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 $C_{18}H_{25}ClN_3O$, 334.2]; LC/MS retention time (method B): t_R = 1.49 min.

Example 239

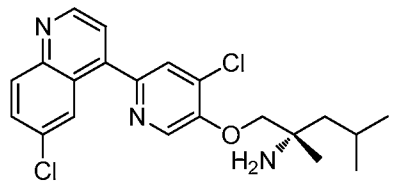
(*S*)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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-NH_2)$^+$, calcd $C_{12}H_{16}Cl_2NO$, 260.1]; LC/MS retention time (method B): t_R = 1.73 min.



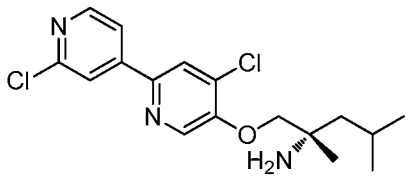
Part B: (S)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

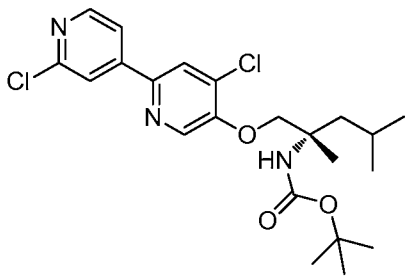
Suzuki coupling was performed as described in Example 193. Obtained (*S*)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (8.4 (*S*)-1-((4-chloro-6-(6-chloroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (mg, 0.020 mmol, 22% yield over two steps). ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{21}H_{24}Cl_2N_3O$, 404.1]; LC/MS retention time (method B): t_R = 1.91 min.

Example 240

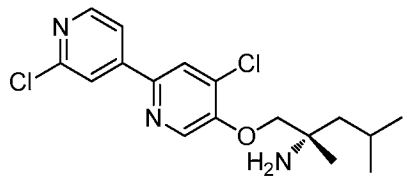
(*S*)-1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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.



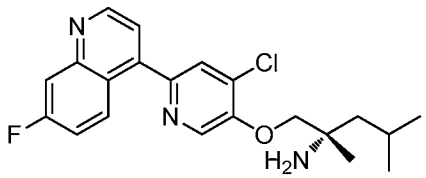
Part B: (S)-1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

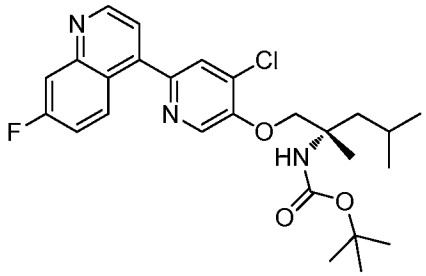
TFA deprotection as described in Example 32. Obtained (*S*)-1-((2',4-dichloro-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (4.9 mg, 0.014 mmol, 100% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.51 (d, *J*=5.5 Hz, 1H), 8.44 (s, 1H), 8.15 (s, 1H), 8.08 (dd, *J*=5.1, 1.5 Hz, 1H), 1.82 (dquin, *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.

Example 241

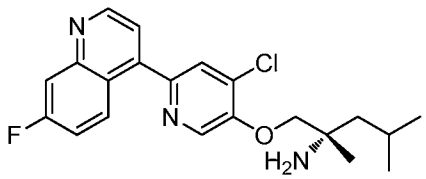
(*S*)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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 $C_{26}H_{32}ClFN_3O_3$, 488.2]; LC/MS retention time (method B): t_R = 2.37 min.



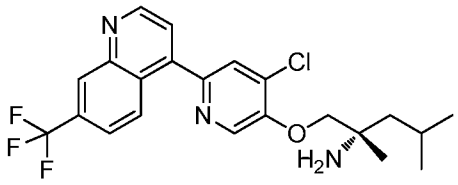
Part B: (S)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

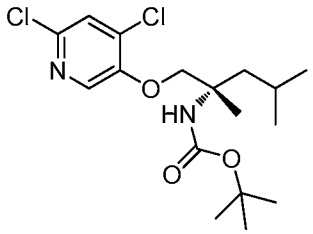
TFA deprotection as described in Example 32. Obtained (*S*)-1-((4-chloro-6-(7-fluoroquinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (4.4 mg, 0.011 mmol, 18% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.01 (d, *J*=4.4 Hz, 1H), 8.68 (s, 1H), 8.33 (dd, *J*=9.4, 6.4 Hz, 1H), 8.01 (s, 1H), 7.85 (dd, *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 $C_{21}H_{24}ClFN_3O$, 388.2]; LC/MS retention time (method B): t_R = 1.82 min.

Example 242

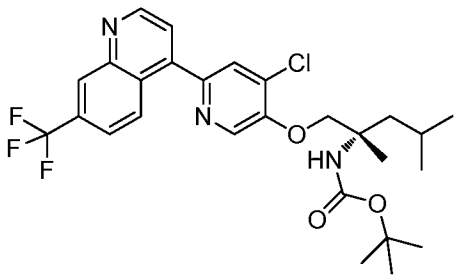
(*S*)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





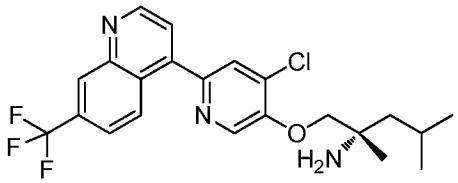
Part A: (S)-tert-butyl (1-((4,6-dichloropyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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). ^{1}H 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 $C_{17}H_{26}Cl_2NaN_2O_3$, 399.1]; LC/MS retention time (method B): t_R = 2.41 min.



Part B: (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 193. 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.

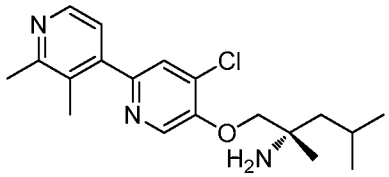


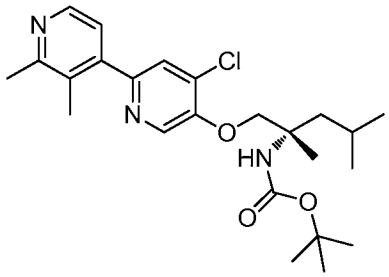
Part C: (S)-1-((4-chloro-6-(7-(trifluoromethyl)quinolin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

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). ^{1}H 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

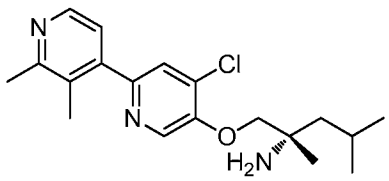
(*S*)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





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 193. 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 $C_{24}H_{35}ClN_3O_3$, 448.2]; LC/MS retention time (method B): t_R = 2.14 min.

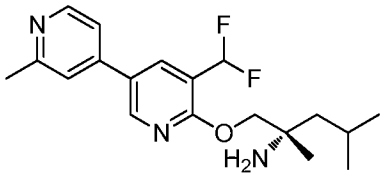


Part B: (S)-1-((4-chloro-2',3'-dimethyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

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 μmol, 8% yield). ^{1}H NMR (500MHz, DMSO-d_6) 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 $C_{19}H_{27}ClN_3O$, 348.2]; LC/MS retention time (method B): t_R = 1.34 min.

Example 244

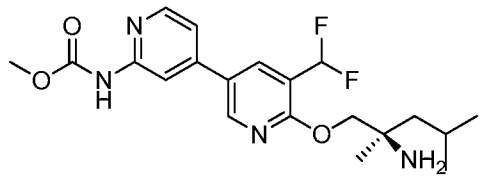
(*S*)-1-((5-(difluoromethyl)-2'-methyl-[3,4'-bipyridin]-6-yl)oxy)-2,4-dimethylpentan-2-amine



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). ^{1}H NMR (500MHz, DMSO-d$_6$) 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.

Example 245

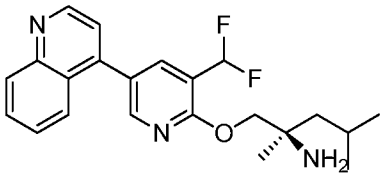
(*R*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate

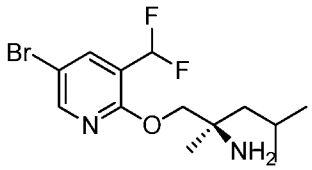


Suzuki coupling was performed as described in Example 193. Obtained (*R*)-methyl (6-((2-amino-2,4-dimethylpentyl)oxy)-5-(difluoromethyl)-[3,4'-bipyridin]-2'-yl)carbamate (13.3 mg, 0.032 mmol, 54% yield). ^{1}H NMR (500MHz, DMSO-d$_6$) δ 8.69 (s, 1H), 8.35 (d, *J*=5.1 Hz, 1H), 8.22 (s, 1H), 8.11 (s, 1H), 7.44 (d, *J*=3.7 Hz, 1H), 7.39 - 7.14 (t, *J*=44.0Hz, 1H), 4.15 (d, *J*=2.6 Hz, 2H), 3.71 (s, 3H), 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

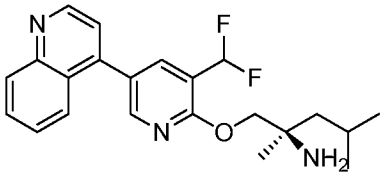
(R)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





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.

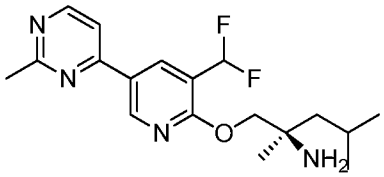


Part B: (R)-1-((3-(difluoromethyl)-5-(quinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

Suzuki coupling was performed as described in Example 193. 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). ^{1}H 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.

Example 247

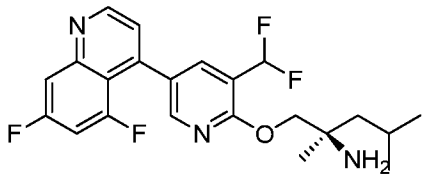
(*R*)-1-((3-(difluoromethyl)-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Suzuki coupling was performed as described in Example 193. 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). ^{1}H 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-NH_2)$^+$, calcd $C_{18}H_{22}F_2N_3O$, 334.2]; LC/MS retention time (method B): t_R = 1.81 min.

Example 248

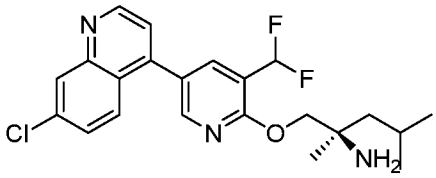
(*R*)-1-((3-(difluoromethyl)-5-(5,7-difluoroquinolin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine



Suzuki coupling was performed as described in Example 193. 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). ^{1}H NMR (500MHz, DMSO-d_6) 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-NH_2)$^+$, calcd $C_{22}H_{21}F_4N_2O$, 405.2]; LC/MS retention time (method B): t_R = 2.01 min.

Example 249

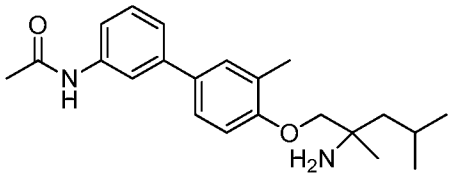
(*R*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

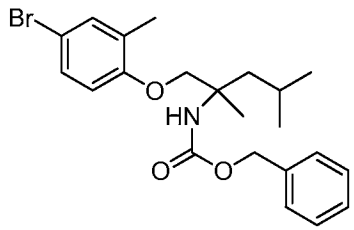


Suzuki coupling was performed as described in Example 193. Obtained (*R*)-1-((5-(7-chloroquinolin-4-yl)-3-(difluoromethyl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (16.9 mg, 0.039 mmol, 34% yield). ^{1}H NMR (500MHz, DMSO-d_6) δ 9.01 (d, *J*=4.4 Hz, 1H), 8.52 (s, 1H), 8.19 (d, *J*=2.2 Hz, 1H), 8.16 (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), 7.42 - 7.16 (t, *J*=55.0Hz, 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.

Example 250

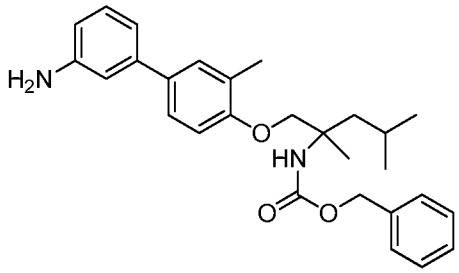
N-(4'-((2-amino-2,4-dimethylpentyl)oxy)-3'-methyl-[1,1'-biphenyl]-3-yl)acetamide





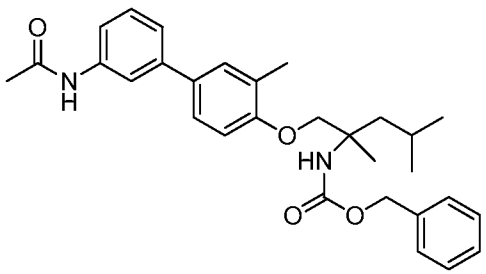
Part A: Benzyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

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.



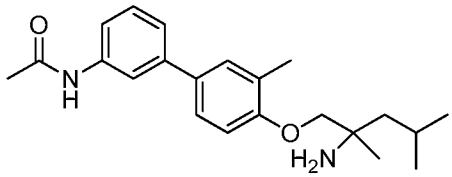
Part B: Benzyl (1-((3'-amino-3-methyl-[1,1'-biphenyl]-4-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

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). ^{1}H 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.

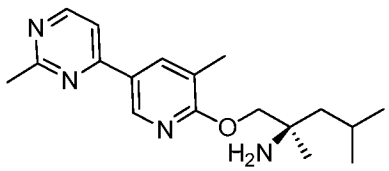


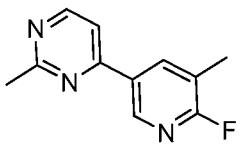
Part D: N-(4'-((2-amino-2,4-dimethylpentyl)oxy)-3'-methyl-[1,1'-biphenyl]-3-yl)acetamide

A mixture of Pd/C (3 mg, 2.82 μmol) 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 diatomaceous earth pad (Celite®) 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. ^{1}H NMR (500MHz, DMSO-d_6) 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 $[(M-NH_2)^+$, calcd $C_{22}H_{28}NO_2$, 338.2]; LC/MS retention time (method A): t_R = 2.03 min.

Example 263

(*R*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine

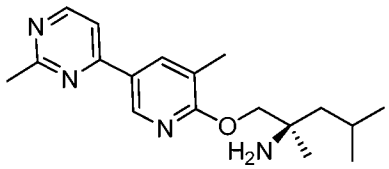




Part A: 4-(6-fluoro-5-methylpyridin-3-yl)-2-methylpyrimidine

A stirred solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), Cs_2CO_3 (507 mg, 1.556 mmol), (6-fluoro-5-methylpyridin-3-yl)boronic acid (121

mg, 0.778 mmol) in a mixture of 1,4-dioxane (6 mL) and water (0.5 mL) was purged with nitrogen for 3 min. XPhos 2nd generation precatalyst (61.2 mg, 0.078 mmol) was added in one portion and the reaction mixture was heated to 80 °C and stirred for 1 h. The reaction mixture was allowed to cool to room temperature. Water (20 mL) was added and the solution was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc in hexanes) to afford 4-(6-fluoro-5-methylpyridin-3-yl)-2-methylpyrimidine (115 mg, 0.521 mmol, 67% yield) as an off-white solid. LCMS (ESI) *m/e* 204.2 [$(M+H)^+$, calcd for $C_{11}H_{11}FN_3$, 204.1]; LC/MS retention time (method A1) t_R = 1.90 min.

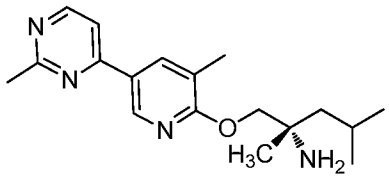


Part B: (R)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine

To a stirred solution of 4-(6-fluoro-5-methylpyridin-3-yl)-2-methylpyrimidine (15 mg, 0.068 mmol) and (*R*)-2-amino-2,4-dimethylpentan-1-ol (8.91 mg, 0.068 mmol) in DMF (0.6 mL) was added cesium carbonate (22.13 mg, 0.068 mmol) under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was diluted with MeOH (2 mL) and filtered through diatomaceous earth (Celite®) washing with MeOH. The filtrate was concentrated under reduced pressure. The crude material was purified via preparative LC/MS using method-A to afford (*R*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine (3 mg, 8.59 µmol, 13% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, METHANOL-*d4*) δ 8.79 (dd, *J* = 0.6, 2.4 Hz, 1H), 8.66 (d, *J* = 5.5 Hz, 1H), 8.37 - 8.27 (m, 1H), 7.77 (dd, *J* = 0.5, 5.5 Hz, 1H), 4.32 (s, 2H), 2.75 (s, 3H), 2.37 (s, 3H), 1.88 -1.85 (m, 1H), 1.65 (d, *J* = 5.5 Hz, 1H), 1.62 - 1.54 (m, 1H), 1.33 (s, 3H), 1.02 (m, 6H) ppm. LCMS (ESI) *m/e* 315.2 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$, 315.2]; LC/MS retention time (method I) t_R = 1.05 min. LCMS (ESI) *m/e* 315.2 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$, 315.2]; LC/MS retention time (method H) t_R = 1.26 min.

Example 268

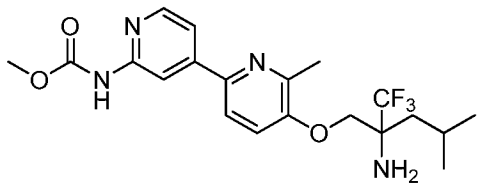
(*S*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine

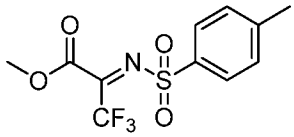


To a stirred solution of 4-(6-fluoro-5-methylpyridin-3-yl)-2-methylpyrimidine (50 mg, 0.226 mmol) (prepared as described in Example 263) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (29.7 mg, 0.226 mmol) in THF (3 mL) was added potassium *tert*-butoxide (1M in THF) (0.453 mL, 0.453 mmol) dropwise under a nitrogen atmosphere. The reaction mixture was allowed to stir at ambient temperature for 5 h. The solution was concentrated under reduced pressure. The residue was dissolved in 2 mL of MeOH and purified via preparative LC/MS using method-A to afford (*S*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine (25 mg, 0.053 mmol, 23% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ 8.78 (d, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 5.5 Hz, 1H), 8.34 - 8.28 (m, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 4.27 (s, 2H), 2.74 (s, 3H), 2.36 (s, 3H), 1.86 (s, 1H), 1.58 (dd, *J* = 5.3, 14.8 Hz, 2H), 1.29 (s, 3H), 1.01 (m, 6H). LCMS (ESI) *m/e* 315.2 [(M+H)$^+$, Calcd for $C_{18}H_{27}N_4O$, 315.2]; LC/MS retention time (method H) t_R = 1.94 min. LCMS (ESI) *m/e* 315.2 [(M+H)$^+$, Calcd for $C_{18}H_{27}N_4O$, 315.2]; LC/MS retention time (method I) t_R = 1.57 min.

Example 273

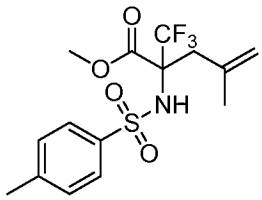
methyl 5-(2-amino-4-methyl-2-(trifluoromethyl)pentyloxy)-6-methyl-2,4'-bipyridin-2'-ylcarbamate





Part A: (Z)-methyl 3,3,3-trifluoro-2-(tosylimino)propanoate

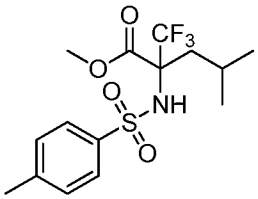
To a stirred solution of 4-methylbenzenesulfonamide (5.49 g, 32.0 mmol) in benzene (50 mL) cooled to 0 °C was added methyl 3,3,3-trifluoro-2-oxopropanoate (5 g, 32.0 mmol) stirred for 1h. $SOCl_2$ (2.81 mL, 38.4 mmol) was added dropwise under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 20 min. A solution of pyridine (5.18 mL, 64.1 mmol) in benzene (5 mL) was added dropwise to the reaction mixture at 0 °C and the reaction mixture was allowed to warm to room temperature and stirring continued for 2 h. Pyridine hydrochloride was filtered off, the solvent was evaporated under reduced pressure and the residue was taken for next step without purification. (8 g, 25.9 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-*d* $_6$): δ 7.71-7.73 (m, 2H), 7.35-7.38 (m, 2H), 3.75 (s, 3H), 2.38 (s, 3H) ppm.



Part B: methyl 4-methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl) pent-4-enoate

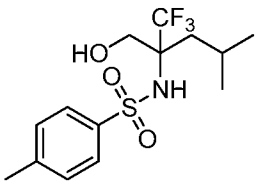
To a nitrogen flushed 1L three necked round bottom flask was added (*E*)-methyl 3,3,3-trifluoro-2-(tosylimino)propionate (5 g, 16.17 mmol) and THF (40 mL). The suspension was cooled to -5 °C with an ice/IPA bath and purged with nitrogen for 5 min. A solution of (2-methylallyl) magnesium chloride in THF (42.0 mL, 21.02 mmol) was added slowly, keeping the temperature below 5 °C. The reaction mixture was allowed to warm to room temperature over a period of 3 h. The reaction mixture was quenched with a saturated solution of NH_4Cl (100 mL). The organic layer was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered, concentrated in vacuum and the residue was purified by silica-gel chromatography (0-20% petroleum ether/ethyl acetate) to give methyl 4-methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl) pent-4-enoate (2.5 g, 6.84 mmol, 42% yield) as a off-white semi-solid which was used for the next step without further purification. ^{1}H NMR (400

MHz, DMSO-*d*6): δ 8.77 (s, 1H), 7.69 (d, *J* = 8.40 Hz, 2H), 7.38 (d, *J* = 8.00 Hz, 2H), 4.74-4.85 (m, 2H), 3.63 (s, 3H), 2.64-2.70 (m, 2H), 2.39 (s, 3H), 1.57 (s, 3H) ppm.



Part C: 4-Methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl) pentanoate

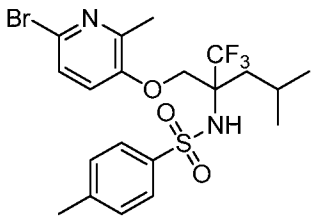
To a stirred solution of methyl 4-methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl) pent-4-enoate (1 g, 2.63 mmol) in MeOH (5 mL),Pd/C (0.280 g, 2.63 mmol) was added in portions to the reaction mixture under a nitrogen atmosphere. The reaction mixture was stirred at room temperature under hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was diluted with methanol (50 mL), filtered through diatomaceous earth (Celite®), and the bed was washed with methanol (30 mL). The filtrate was concentrated under reduced pressure to afford methyl 4-methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl) pentanoate (0.92 g, 2.454 mmol, 93% yield) as a colorless oil which was carried forward without further purification. LCMS (ESI) *m/e* 366.0 [(M-H)$^-$, calcd for $C_{15}H_{19}F_3NO_4S$ 366.1]; LC/MS retention time (method A2): t_R = 2.34 min.



Part D: 4-methyl-N-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide

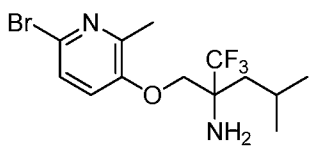
A solution of methyl 4-methyl-2-(4-methylphenylsulfonamido)-2-(trifluoromethyl)pentanoate (0.15 g, 0.408 mmol) in THF (5 mL) was cooled at 0°C. LAH in THF (0.163 mL, 0.408 mmol) was added dropwise and the mixture stirred for 10 min. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction mixture was allowed to cool to 0°C and saturated sodium sulfate solution was added dropwise until completion of effervescence. The reaction

mixture was filtered and the filtrate were dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide as colorless oil which was carried forward without further purification. LCMS (ESI) *m/e* 338.2 [(M-H)$^-$, calcd for $C_{14}H_{19}F_3NO_3S$ 338.1]; LC/MS retention time (method A2): t_R = 2.07 min.



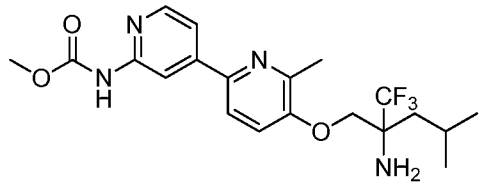
Part E: N-(2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-yl)-4-methylbenzenesulfonamide

To a solution of 4-methyl-*N*-(1, 1, 1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2 yl) benzene sulfonamide (0.1 g, 0.295 mmol) in DMF (4 mL) cooled at 0 °C was added NaH (7.07 mg, 0.295 mmol) followed by slow addition of 6-bromo-3-fluoro-2-methylpyridine (0.062 g, 0.324 mmol). The reaction mixture was stirred for 5 min at 0 °C then allowed to stir at 80 °C for 4 h. The reaction mixture was quenched with water (20 mL). The reaction mixture was diluted with ethyl acetate (20 mL) and the organic layer was separated out. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a brown color solid that was purified by silica-gel chromatography (pet ether/ethyl acetate) to afford *N*-(2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (70 mg, 0.137 mmol, 47% yield) as a brown color solid which was carried forward without further purification. LCMS (ESI) *m/e* 509.1 (bromo pattern) [(M+H)$^+$, calcd for $C_{20}H_{25}BrF_3N_2O_3S$ 509.1]; LC/MS retention time (method A2): t_R = 2.45 min.



Part F: 2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-amine

A 50 mL round bottom flask containing *N*-(2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (45 mg, 0.088 mmol) was cooled at 0°C and sulfuric acid (2 mL, 37.5 mmol) was added dropwise to the reaction mixture. The reaction mixture was allowed to stir at 0°C for 2 h. The reaction mixture was poured into saturated sodium bicarbonate solution (pH~8-9) and extracted with ethyl acetate(3 x 20 mL). The combined the organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude 2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-amine (crude yield) (25 mg, 0.070 mmol, 80% yield) as a brown semi-solid which was carried forward without further purification. LCMS (ESI) *m/e* 355.0 [$(M+H)^+$, calcd for $C_{13}H_{19}BrF_3N_2O$ 355.1]; LC/MS retention time (method A2): t_R = 2.84 min.



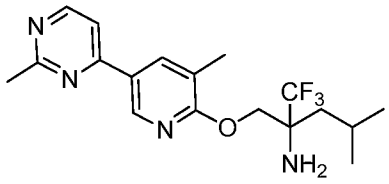
Part G: Methyl 5-(2-amino-4-methyl-2-(trifluoromethyl)pentyloxy)-6-methyl-2,4'-bipyridin-2'-ylcarbamate

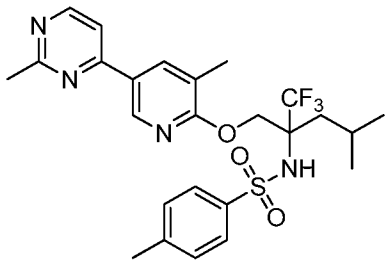
A solution of methyl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)carbamate (30 mg, 0.108 mmol), 2-(((6-bromo-2-methylpyridin-3-yl)oxy)methyl)-1,1,1-trifluoro-4-methylpentan-2-amine (38.3 mg, 0.108 mmol), and Cs_2CO_3 in water (0.108 mL, 0.216 mmol) and 1,4-dioxane (5 mL) was purged with nitrogen gas for 10 min. $PdCl_2$(dppf)-CH_2Cl_2 adduct (8.81 mg, 10.79 µmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated, dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford methyl 5-(2-amino-4-methyl-2-

(trifluoromethyl)pentyloxy)-6-methyl-2,4'-bipyridin-2'-ylcarbamate (11 mg, 0.025 mmol, 24% yield) as a pale yellow solid. LCMS (ESI) *m/e* 427.2 [$(M+H)^+$, calcd for $C_{20}H_{26}F_3N_4O_3$ 427.2]; LC/MS retention time (method H): t_R = 2.68 min. ^1H NMR(400 MHz, methanol: δ 8.33 (d, *J* = 6.40 Hz, 1H), 8.24 (s, 1H), 7.97-8.02 (m, 2H), 7.59 (d, *J* = 8.80 Hz, 1H), 4.42-4.53 (m, 2H), 3.91 (s, 3H), 2.61 (s, 3H), 1.96-2.03 (m, 3H), 1.05-1.09 (m, 6H) ppm.

Example 274

1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-amine

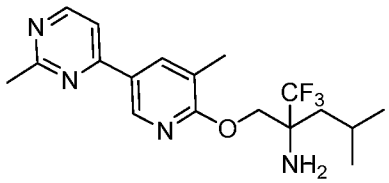




Part A: 4-methyl-N-(1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide

To a stirred solution of 4-(6-fluoro-5-methylpyridin-3-yl)-2-methylpyrimidine (40 mg, 0.197 mmol) (prepared as described in Example 263) and 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide (66.8 mg, 0.197 mmol) (prepared as described in Example 273) in tetrahydrofuran (5 mL) was added potassium *tert*-butoxide (44.2 mg, 0.394 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature for 12 h. The solution was concentrated under reduced pressure. Water (15 mL) was added and the solution was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep. TLC using a mobile phase of (30% EtOAc in hexanes). Required product band was

collected and stirred in DCM (25 mL), passed through a diatomaceous earth (Celite®) pad and the pad was washed with DCM (20 mL). The combined filtrate was evaporated to dryness under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide (65 mg, 0.037 mmol, 19% yield) as yellow oil. The product was carried forward without further purification. LCMS (ESI) *m/e* 523.6 [(M+H)$^+$, calcd for $C_{25}H_{30}F_3N_4O_3S$, 523.2]; LC/MS retention time (method B) t_R = 1.12 min.

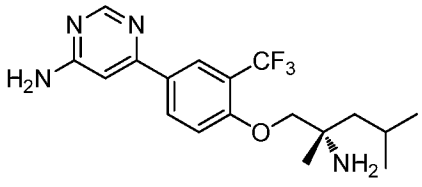


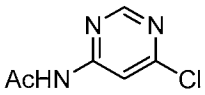
Part B. 1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-amine

To a stirred solution of 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide (45 mg, 0.026 mmol) in sulfuric acid (2 mL) was stirred for 2 h. The reaction mixture was poured slowly into saturated aq. sodium bicarbonate solution and the pH was adjusted to 8, The solution was extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via preparative LC/MS using method-B to afford 1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-amine (5 mg, 0.013 mmol, 52% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.76 (s,1H), 8.62 (d, *J*=5.02 Hz, 1H), 8.29 (s, 1H), 7.74 (d, *J*=5.52 Hz, 1H), 4.46(m, 2H) 3.7 (s, 3H), 2.2 (s, 3H), 1.9 (m, 1H), 1.8 (m, 1 H), 1.6 (m, 1H) 0.9 - 1.1 (m, 6H) ppm. LCMS (ESI) *m/e* 369.2 [(M+H)$^+$, calcd for $C_{18}H_{24}F_3N_4O$, 369.2]; LC/MS retention time (method I) t_R = 2.17 min. LCMS (ESI) *m/e* 369.2 [(M+H)$^+$, calcd for $C_{18}H_{24}F_3N_4O$, 369.2]; LC/MS retention time (method H) t_R = 2.88 min.

Example 278

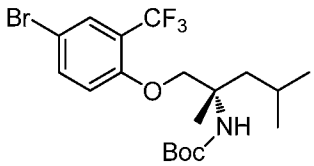
(*S*)-6-(4-((2-amino-2, 4-dimethylpentyl) oxy)-3-(trifluoromethyl) phenyl) pyrimidin-4-amine





Part A. N-(6-chloropyrimidin-4-yl) acetamide

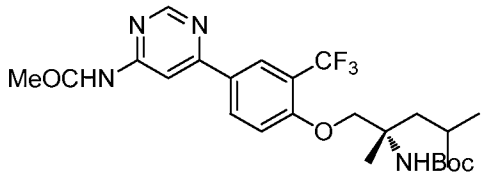
A mixture of 4,6-dichloropyrimidine (1.0 g, 6.71 mmol), acetamide (0.396 g, 6.71 mmol), Cs_2CO_3 (4.37 g, 13.42 mmol), $PdOAc_2$ (0.060 g, 0.268 mmol) and XANTPHOS (0.350 g, 0.604 mmol) in 1,4-dioxane (5 mL) was heated at 75 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (15 mL) and extracted with ethyl acetate (2x20 mL). The ethyl acetate layer was collected, washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford *N*-(6-chloropyrimidin-4-yl)acetamide (0.75 g, 4.24 mmol, 63% yield) as a brown solid. LCMS (ESI) *m/e* 172.0 [$(M+H)^+$, calcd for $C_6H_7ClN_3O$ 172.0]; LC/MS retention time (method B): t_R = 0.57 min.



Part B: (S)-Tert-butyl (1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

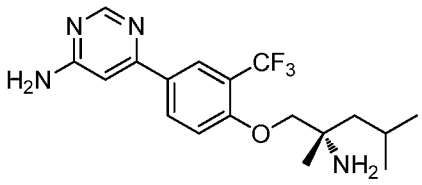
To a mixture of 4-bromo-2-(trifluoromethyl) phenol (4 g, 16.60 mmol) in DMF (50 mL) cooled at 0 °C, was added K_2CO_3 (6.88 g, 49.8 mmol) in portions followed by slow addition of (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (5.36 g, 18.26 mmol) in 10 mL DMF. The reaction mixture was slowly allowed to warm to room temperature then stirred at 80 °C for 12 h. The reaction mixture was cooled to 0 °C and quenched with aqueous ammonium chloride (100 mL). The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The

organic layer was washed with water (2 x 50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated to afford crude (*S*)-*tert*-butyl (1-(4-bromo-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (6.5 g, 13.16 mmol, 79% yield) as a colorless oil which was carried forward without further purification. ^{1}H NMR (400 MHz, DMSO-d6): δ 7.74-7.81 (m, 2H), 7.19 (d, *J* = 8.80 Hz, 1H), 6.52 (s, 1H), 4.02-4.24 (m, 2H), 1.69-1.80 (m, 2H), 1.41-1.50 (m, 1H), 1.40 (s, 9H), 1.25 (s, 3H), 0.83-0.96 (m, 6H) ppm.



Part C. (S)-tert-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of *N*-(6-chloropyrimidin-4-yl)acetamide (0.03 g, 0.175 mmol), (*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 215, Parts A and B) (0.063 g, 0.125 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (10.20 mg, 0.012 mmol) and Cs_2CO_3 (0.122 g, 0.375 mmol) in 1,4-dioxane (2 mL) was heated at 80 ° C overnight. The solution was cooled to room temperature and concentrated under reduced pressure. Water (50 mL) was added and the solution was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to (*S*)-*tert*-butyl(1-(4-(6-acetamidopyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.076 mmol, 61% yield) as semi-solid which was carried forward without further purification. LCMS (ES-API) *m/e* 511.2 [$(M+H)^+$, calcd for $C_{25}H_{34}F_3N_4O_4$, 511.2]; LC/MS retention time (method D): t_R = 2.54 min.

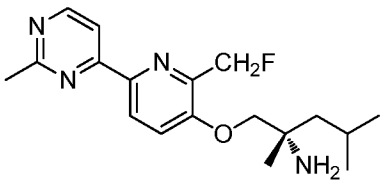


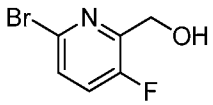
Part D: (S)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-(trifluoromethyl) phenoxy)-2, 4-dimethylpentan-2-yl) carbamate (0.05 g, 0.098 mmol) in MeOH (2 mL) at 0 °C, 4N HCl in 1,4-dioxane (0.245 mL, 0.979 mmol) was added and stirred for 1 h. The reaction mixture was concentrated under reduced pressure to afford (*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-amine (0.01 g, 0.027 mmol, 27% yield) as a pale yellow solid which was carried forward without further purification. LCMS (ESI) *m/e* 369.0 [$(M+H)^+$, calcd for $C_{18}H_{24}F_3N_4O$, 369.2]; LCMS retention time (method F): t_R = 1.37 min; LCMS retention time (method G): t_R = 0.81 min. ^1H NMR (400 MHz, *CD3OD*): δ 8.61 (s, 1H), 8.20 (m, 2H), 7.53 (d, *J* = 8.80 Hz, 1H), 7.03 (d, *J* = 0.80 Hz, 1H), 4.29-4.37 (m, 2H), 1.85-1.92 (m, 2H), 1.71-1.77 (m, 1H), 1.55 (s, 3H), 1.02-1.08 (m, 6H) ppm.

Example 279

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

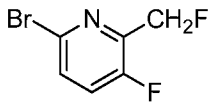




Part A. (6-bromo-3-fluoropyridin-2-yl)methanol

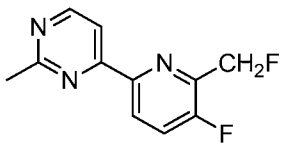
To a solution of 6-bromo-3-fluoropicolinaldehyde (1.7 g, 8.33 mmol) in methanol (20 mL) at 0 °C was added $NaBH_4$ (0.473 g, 12.50 mmol). The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL), saturated NaCl (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated

under reduced pressure to afford (6-bromo-3-fluoropyridin-2-yl)methanol (1.6 g, 7.53 mmol, 90% yield) was isolated as a brown solid. LCMS (ESI) *m/e* 205.9 (bromo pattern) [$(M+H)^+$, calcd for C_6H_6BrFNO, 205.9]; LC/MS retention time (Method C): t_R = 0.56 min.



Part B. 6-bromo-3-fluoro-2-(fluoromethyl)pyridine

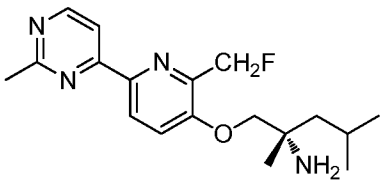
A solution of (6-bromo-3-fluoropyridin-2-yl)methanol (800 mg, 3.88 mmol) in dichloromethane (15 mL) was cooled to -20 °C and DAST (1.539 mL, 11.65 mmol) was added. The reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with saturated sodium bicarbonate (10 mL), extracted with dichloromethane(2 x 25 mL). The dicholormethane layer was washed with water (1 x 20 mL), saturated NaCl (1 x 20 mL),was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified on silica gel chromatography (0-35% petroleum ether in ethyl acetate) to afford 6-bromo-3-fluoro-2-(fluoromethyl)pyridine (500 mg, 2.40 mmol, 62% yield) as a brown solid. GCMS (ESI) *m/e* 207.0 [$(M)^+$, calcd for $C_6H_7BrF_2N$, 207.0]; GC/MS retention time (method E): t_R = 6.52 min.



Part C. 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-2-methylpyrimidine

A solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), hexamethylditin (129 µl, 0.622 mmol), tetrakis(triphenylphosphine)palladium (0) (44.9 mg, 0.039 mmol) and 6-bromo-3-fluoro-2-(fluoromethyl)pyridine (113 mg, 0.544 mmol) in 1,4-dioxane was purged with nitrogen and irradiated in a microwave at 120 °C for 1 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. The black residue was purified

via silica gel chromatography (0-25% petroleum ether in ethyl acetate) to afford 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-2-methylpyrimidine (35 mg, 0.123 mmol, 16% yield) as a brown semi-solid. LCMS (ESI) *m/e* 222.9 [$(M+H)^+$, calcd for $C_{11}H_{10}F_2N_3$, 222.1]; LC/MS retention time (Method C): t_R = 0.81 min.

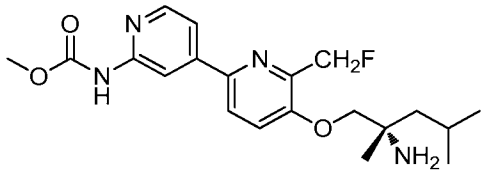


Part D. (S)-1-((2-(fluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-2-methylpyrimidine (35 mg, 0.158 mmol) in THF (3 mL) at 0 °C was added 1 M potassium *tert*-butoxide in THF (0.237 mL, 0.237 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol. The reaction mixture was allowed to stir for 2 h at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 10 mL), saturated NaCl (1 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The brown semi-solid residue was purified on silica gel chromatography (0-10% MeOH in DCM) to afford (*S*)-1-((2-(fluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (23 mg, 0.062 mmol, 39% yield) as a pale yellow semi-solid. LCMS (ESI) *m/e* 333.2[$(M+H)^+$, calcd for $C_{18}H_{26}FN_4O$ 333.41]; LC/MS retention time (Method G) t_R = 1.63 min. ^1H NMR (400 MHz, Methanol-*d4*): δ 8.73 (d, *J*=5.40 Hz, 1H) 8.57 (dd, *J*=8.72, 1.69 Hz, 1H) 8.22 (dd, *J*=5.40, 0.50 Hz, 1H) 7.65 (d, *J*=8.53 Hz, 1H) 5.70 (d, *J*=1.95 Hz, 1H) 5.58 (d, *J*=1.88 Hz, 1H) 3.94 - 4.04 (m, 2H) 2.77 (s, 3H) 1.80 - 1.93 (m, 1H) 1.52 - 1.69 (m, 2H) 1.29 - 1.31 (m, 3H) 0.99 - 1.04 (m, 6H) ppm.

Example 280

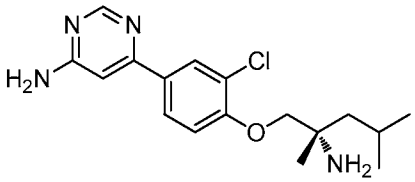
(*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate

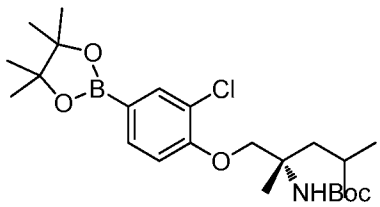


Prepared in a similar fashion as described in Example 279. (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)-[2,4'-bipyridin]-2'-yl)carbamate. TFA (46 mg, 0.089 mmol, 58% yield) as a pale yellow solid. LCMS (ESI) *m/e* 391.3 [(M+H)$^+$, calcd for $C_{20}H_{28}FN_4O_3$·TFA 391.2]; LC/MS retention time (method H): t_R = 1.32 min; LC/MS retention time (method I): t_R = 1.36 min. ^{1}H NMR(400 MHz, Methanol-*d*4): δ 8.43 - 8.29 (m, 2H), 8.22 - 8.14 (m, 1H), 7.98 - 7.89 (m, 1H), 7.71-7.73 (d, *J*=9.0 Hz, 1H), 5.84 - 5.56 (m, 2H), 4.38 - 4.29 (m, 1H), 4.27 - 4.20 (m, 1H), 3.90 (s, 3H), 1.90 (s, 2H), 1.80 - 1.68 (m, 1H), 1.55 (s, 3H), 1.13 - 1.00 (m, 6H) ppm.

Example 285

(*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-4-amine

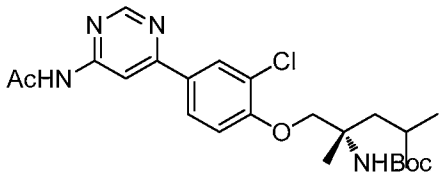




Part A. (S)-tert-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

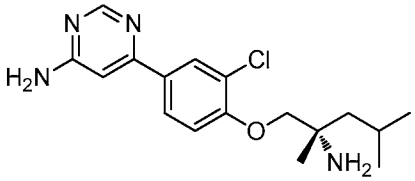
A mixture of (*S*)-*ter*t-butyl (1-(4-bromo-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (1.2 g, 2.85 mmol), *bis*(pinacolato)diboron (0.797 g, 3.14 mmol), potassium acetate (0.840 g, 8.56 mmol and $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.116 g, 0.143 mmol) in 1,4-dioxane (20 mL) was heated at 90 °C overnight. The reaction mixture was filtered through celite and the celite bed was washed with ethyl acetate (100 mL). The organic layer was washed with water (50 mL). The aqueous layer was re-extracted with ethyl acetate (2x50 mL). The organic layer was

collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (1.2 g, 2.57 mmol, 90% yield) as colorless liquid. ^{1}H NMR (400 MHz, *CDCl3*): δ 7.78 (d, *J* = 1.60 Hz, 1H), 7.61-7.63 (m, 1H), 6.91 (d, *J* = 8.00 Hz, 1H), 4.10-4.19 (m, 1H), 4.63 (s, 1H), 4.02 (d, *J* = 8.80 Hz, 1H), 1.79-1.87 (m, 2H), 1.57-1.62 (m, 1H), 1.51 (s, 3H), 1.33-1.41 (m, 12H), 0.96-0.98 (m, 6H) ppm.



Part B. (S)-tert-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of *N*-(6-chloropyrimidin-4-yl)acetamide (prepared as described in Example 278) (0.03 g, 0.175 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate) (0.058 g, 0.125 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (10.20 mg, 0.012 mmol) and Cs_2CO_3 (0.122 g, 0.375 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The solution was concentrated under reduced pressure. Water (15 mL) was added and the solution was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc in hexanes) to afford (*S*)-*tert*-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-chlorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.093 mmol, 75% yield) as a semi-solid. LCMS (ESI) *m/e* 475.9 [$(M-H)^-$, calcd for $C_{24}H_{32}ClN_4O_4$ 475.2]; LC/MS retention time (method A2): t_R = 2.43 min.



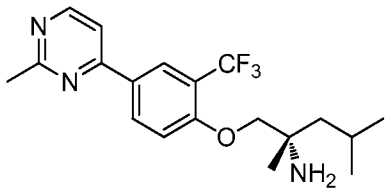
Part C. (S)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-4-

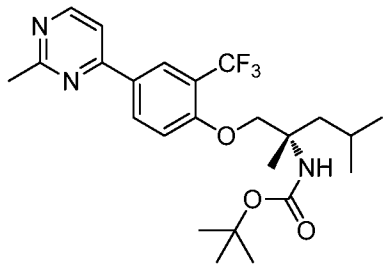
amine

To a solution of (*S*)-*tert*-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-chlorophenoxy)-2, 4-dimethylpentan-2-yl) carbamate (0.05 g, 0.105 mmol) in MeOH (2 mL) cooled to 0° C was added 4N HCl in 1,4-dioxane (0.262 mL, 1.048 mmol). The mixture was stirred for 1h at room temperature. The crude material was purified by prep LC/MS (method A) to afford (*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-4-amine (0.026 g, 0.077 mmol, 73% yield) as a pale yellow solid. LCMS (ESI) *m/e* 335.0 [(M+H)$^+$, calcd for $C_{17}H_{24}ClN_4O$ 335.2]; LCMS retention time (method F): t_R = 1.17 min; LCMS retention time (method G): t_R = 0.73 min. ^{1}H (400 MHz, *CD3OD*): δ 8.61 (d, *J* = 0.80 Hz, 1H), 8.03 (d, *J* = 2.00 Hz, 1H), 7.87 (d, *J* = 10.80 Hz, 1H), 7.42 (d, *J* = 8.80 Hz, 1H), 6.99 (d, *J* = 0.40 Hz, 1H), 4.25-4.32 (m, 2H), 1.87-1.98 (m, 2H), 1.72-1.76 (m, 1H), 1.55 (s, 3H), 1.03-1.09 (m, 6H) ppm.

Example 290

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

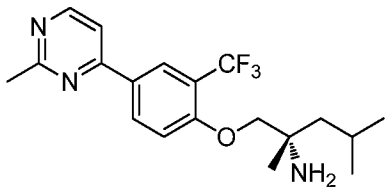




Part A: (S)-tert-butyl (2,4-dimethyl-1-(4-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate

A mixture of 4-chloro-2-methylpyrimidine (0.035 g, 0.272 mmol), (*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

215, Parts A and B) (0.137 g, 0.272 mmol), potassium phosphate (tribasic) (0.058 g, 0.272 mmol), and KBr (0.032 g, 0.272 mmol) were taken in 1,4-dioxane (10 mL). The reaction mixture was purged with nitrogen gas for 30 min and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.022 g, 0.027 mmol) was added. The reaction mixture was again purged with nitrogen gas for another 10 min and heated at 80 °C for 2 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (20 mL) and ethyl acetate (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL) and the ethyl acetate layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.06 g, 0.128 mmol, 47% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 468.2 [$(M+H)^+$, calcd for $C_{24}H_{33}F_3N_3O_3$ 468.2]; LC/MS retention time (Method A1): t_R = 3.51 min.



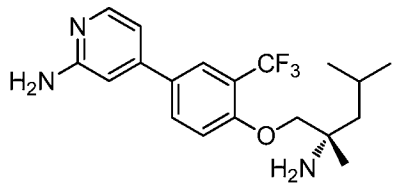
Part B: (S)-2,4-dimethyl-1-(4-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

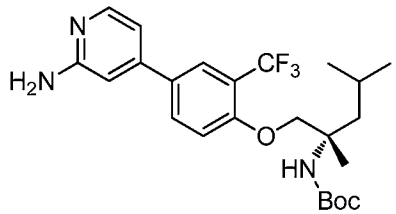
To a solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.06 g, 0.128 mmol) in dichloromethane (2 mL) at 0 °C was added TFA (0.198 mL, 2.57 mmol) and the mixture stirred for 5min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method B) to afford (*S*)-2,4-dimethyl-1-(4-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (39.2 mg, 0.061 mmol, 47% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.0 [$(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$ 368.2]; LC/MS retention time (method H): t_R = 1.67 min; LC/MS retention time (method I): t_R = 1.12 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.71 (d, *J* = 5.60 Hz, 1H), 8.46-8.53 (m, 2H), 7.85 (d, *J* = 5.60 Hz, 1H), 7.43 (d, *J* =

8.80 Hz, 1H), 4.25-4.33 (m, 2H), 2.76 (s, 3H), 1.84-1.91 (m, 2H), 1.69-1.75 (m, 1H), 1.53 (s, 3H), 1.01-1.06 (m, 6H) ppm.

Example 297

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-amine

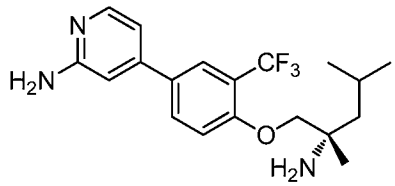




Part A: (S)-tert-butyl (1-(4-(2-aminopyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of 4-chloropyridin-2-amine (0.2 g, 1.556 mmol) in THF (30 mL) was added (*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 215, Parts A and B) (0.780 g, 1.56 mmol) and potassium phosphate, dibasic (2.33 mL, 4.67 mmol). The reaction mixture was purged with argon for 10 min and XPhos 2nd generation precatalyst (0.061 g, 0.078 mmol) was added. The reaction mixture was again purged with argon for 10 min and heated for 3 h at 65°C. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL) and water (10 mL) and the organic layer was separated. The aqueous layer was again extracted with ethyl acetate (2x18 mL). The combined ethyl acetate layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by Preparative TLC (70% ethyl acetate in hexanes). The required spot was collected, dissolved in 40 mL of 5% MeOH in DCM, filtered and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-(2-aminopyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.375 g, 0.798 mmol, 51% yield) as an off-white solid. LCMS (ESI)

m/e 468.4 [(M+H)$^+$, calcd for $C_{24}H_{33}F_3N_3O_3$, 468.2]; LC/MS retention time (Method A1): t_R = 2.38 min.

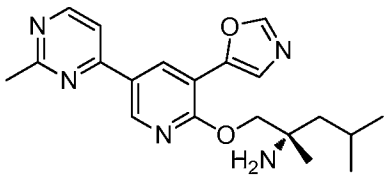


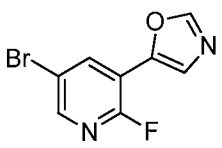
Part B: (S)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-amine

To a solution (*S*)-*tert*-butyl (1-(4-(2-aminopyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.050 g, 0.106 mmol) in dichloromethane (1 mL) at 0 °C was added TFA (0.5 μL, 6.49 μmol). The reaction mixture was allowed to stir for 2 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-amine (0.019 g, 0.051 mmol, 48% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.2 [(M+H)$^+$, calcd for $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method H): t_R = 1.54 min; LC/MS retention time (method I): t_R = 0.99 min. ^{1}H NMR (400 MHz, MeOD): δ 7.95-7.88 (m, 3H), 7.29 (d, *J* = 8.4 Hz, 1H), 6.88-6.82 (m, 2H), 4.03-3.97 (m, 2H), 1.91-1.88 (m, 1H), 1.86-1.79 (m, 2H), 1.30 (s, 3H), 1.0-0.9 (m, 6H) ppm.

Example 298

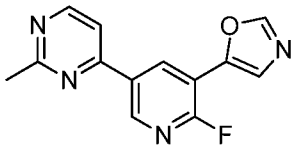
(*S*)-2,4-dimethyl-1-((5-(2-methylpyrimidin-4-yl)-3-(oxazol-5-yl)pyridin-2-yl)oxy)pentan-2-amine





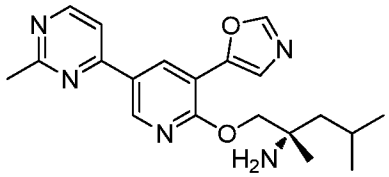
Part A: 5-(5-bromo-2-fluoropyridin-3-yl)oxazole

To a solution of 5-bromo-2-fluoronicotinaldehyde (0.2 g, 0.980 mmol) in methanol (1.25 mL) was added TOSMIC (0.191 g, 0.980 mmol) and K_2CO_3 (0.135 g, 0.980 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated by high vacuum and the residue was diluted with water (2 mL) and ethyl acetate (8 mL). The organic layer was separated and the aqueous layer was again extracted with ethyl acetate (2x10 mL). The combined ethyl acetate layers were washed with saturated sodium bicarbonate solution, brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (40% ethyl acetate in hexanes) to afford 5-(5-bromo-2-fluoropyridin-3-yl)oxazole (0.189 g, 0.732 mmol, 75% yield) as an off-white solid. LCMS (ESI) *m/e* 243.03 [$(M+H)^+$, calcd for $C_8H_5BrFN_2O$, 243.0]; LC/MS retention time (method A1): t_R = 1.79 min.



Part B. 5-(2-fluoro-5-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxazole

A solution of 4-chloro-2-methylpyrimidine (0.050 g, 0.389 mmol), 5-(5-bromo-2-fluoropyridin-3-yl)oxazole (0.100 g, 0.389 mmol) and hexamethylditin (0.097 mL, 0.467 mmol) in 1,4-dioxane (0.1 mL) was purged with argon for 15 min and tetrakis(triphenylphosphine)palladium (0) (0.045 g, 0.039 mmol) was added. The reaction mixture was again purged with argon for 5 min and heated in a microwave for 1 h at 110°C. The reaction mixture was diluted with ethyl acetate (8 mL) and water (5 mL) and the organic layer separated. The aqueous layer was extracted again with ethyl acetate (2x5 mL). The combined ethyl acetate layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The reaction mixture was purified by Preparative TLC (70% ethyl acetate in hexanes). The required spot was collected, dissolved 5% methanol in dichloromethane (30 mL), filtered and concentrated under reduced pressure to afford 5-(2-fluoro-5-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxazole (0.070 g, 0.098 mmol, 25% yield) as an off-white solid. LCMS (ESI) *m/e* 257.0 [$(M+H)^+$, calcd for $C_{13}H_{10}FN_4O$, 257.1]; LC/MS retention time (method B): t_R = 0.86 min.

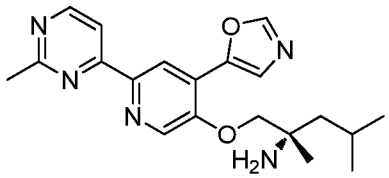


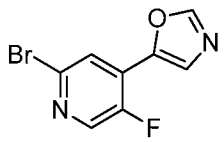
Part C. (S)-2,4-dimethyl-1-((5-(2-methylpyrimidin-4-yl)-3-(oxazol-5-yl)pyridin-2-yl)oxy)pentan-2-amine

To a solution 5-(2-fluoro-5-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxazole (0.076 g, 0.107 mmol) in DMF (0.8 mL) was added (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.014 g, 0.107 mmol) and Cs_2CO_3 (0.070 g, 0.214 mmol) and the reaction mixture was heated at 80 °C for 16 h. To the reaction mixture the chilled water and ethyl acetate (4 mL) was added and stirred for 5 min. The organic layer was separated and the aqueous layer was washed with ethyl acetate (2x3 mL). The combined ethyl acetate layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method B) to afford (*S*)-2,4-dimethyl-1-((5-(2-methylpyrimidin-4-yl)-3-(oxazol-5-yl)pyridin-2-yl)oxy)pentan-2-amine, TFA (0.002 g, 4.04 μmol, 4% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.3 [$(M+H)^+$, calcd for $C_{20}H_{26}N_5O_2$, 368.2]; LC/MS retention time (method H): t_R = 1.25 min; LC/MS retention time (method I): t_R = 0.95 min. ^{1}H NMR (400 MHz, MeOD): δ 8.77 (d, *J* = 2.4 Hz, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.21 (s, 1H), 7.66 (d, *J* = 1.6 Hz, 1H), 7.52 (s, 1H), 4.62 (m, 2H), 2.56 (s, 3H), 1.80-1.65 (m, 2H), 1.48-1.55 (m, 1H), 1.5 (s, 3H), 0.9 (m, 6H) ppm.

Example 299

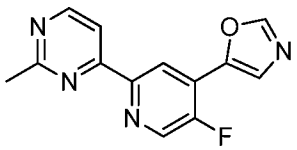
(*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-4-(oxazol-5-yl)pyridin-3-yl)oxy)pentan-2-amine





Part A. 5-(2-bromo-5-fluoropyridin-4-yl)oxazole

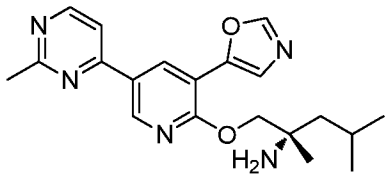
To a solution of 2-bromo-5-fluoroisonicotinaldehyde (0.1 g, 0.490 mmol) in MeOH (2.5 mL) was added TOSMIC (0.096 g, 0.490 mmol) and K_2CO_3 (0.068 g, 0.490 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated by high vacuum and the residue was diluted with water (2 mL) and ethyl acetate (4 mL). The organic layer was separated and aqueous layer was again extracted with ethyl acetate (2x4 mL). The combined ethyl acetate layers were washed with saturated sodium bicarbonate solution, brine, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford 5-(2-bromo-5-fluoropyridin-4-yl)oxazole (0.098 g, 0.382 mmol, 78% yield) as an off-white solid. LCMS (ESI) *m/e* 243.0 [$(M+H)^+$, calcd for $C_8H_5BrFN_2O$ 243.0]; LC/MS retention time (method H): t_R = 1.87 min.



Part B. 5-(5-fluoro-2-(2-methylpyrimidin-4-yl)pyridin-4-yl)oxazole

A solution of 4-chloro-2-methylpyrimidine (0.050 g, 0.389 mmol), 5-(2-bromo-5-fluoropyridin-4-yl)oxazole (0.095 g, 0.389 mmol) and hexamethylditin (0.097 mL, 0.467 mmol) in 1,4-dioxane (0.2 mL) was purged with argon for 15 min and tetrakis(triphenylphosphine)palladium (0) (0.045 g, 0.039 mmol) was added. The reaction mixture was again purged with argon for 5 min and heated in a microwave vial for 1 h at 110°C. The reaction mixture was diluted with ethyl acetate (8 mL) and water(5 mL),separated the organic layer and the aqueous layer was washed with ethyl acetate (2x5 mL). The combined ethyl acetate layers were washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The reaction mixture was purified by Preparative TLC (70% ethyl acetate in hexanes). The required spot was collected, dissolved 5% methanol in dichloromethane (30 mL), filtered and concentrated under reduced pressure to afford

5-(5-fluoro-2-(2-methylpyrimidin-4-yl)pyridin-4-yl)oxazole (0.098 g, 0.099 mmol, 26% yield) as a colorless solid. LCMS (ESI) *m/e* 257.0 [$(M+H)^+$, calcd for $C_{13}H_{10}FN_4O$ 257.1]; LC/MS retention time (method B): t_R = 1.07 min.

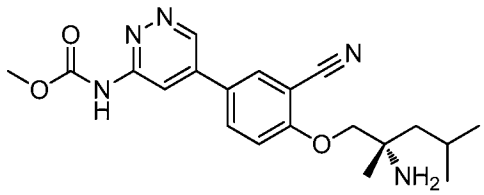


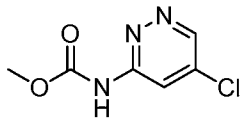
Part C. (S)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-4-(oxazol-5-yl)pyridin-3-yl)oxy)pentan-2-amine

A solution of 5-(5-fluoro-2-(2-methylpyrimidin-4-yl)pyridin-4-yl)oxazole (0.098 g, 0.099 mmol), (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.013 g, 0.099 mmol) and Cs_2CO_3 (0.065 g, 0.199 mmol) in DMF (0.8 mL) was heated at 80 °C for 16 h. To the reaction mixture was added chilled water and ethyl acetate (4 mL) and the mixture stirred for 5 min. The organic layer was separated and the aqueous layer was washed with ethyl acetate (2x3 mL). The combined ethyl acetate layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method C) to afford (*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-4-(oxazol-5-yl)pyridin-3-yl)oxy)pentan-2-amine, TFA (.004 g, 7.63 μmol, 8% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.3 [$(M+H)^+$, calcd for $C_{20}H_{26}N_5O_2$ 368.2]; LC/MS retention time (method H): t_R = 1.29 min; LC/MS retention time (method I): t_R = 0.91 min. ^{1}H NMR (400 MHz, MeOD): δ 8.89 (s, 1H), 8.75 (d, *J* = 5.6 Hz, 1H), 8.66 (s, 1H), 8.46 (s, 1H), 8.2 (d, *J* = 5.6 Hz, 1H), 7.87 (s, 1H), 4.32 (s, 2H), 2.79 (s, 3H), 1.90-1.65 (m, 3H), 1.42 (s, 3H), 1.05 (m, 6H) ppm.

Example 300

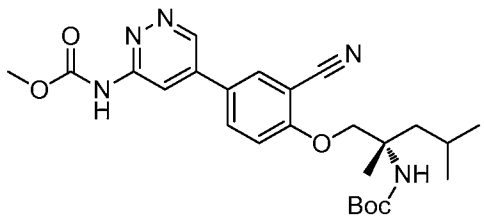
(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate





Part A. methyl (5-chloropyridazin-3-yl)carbamate

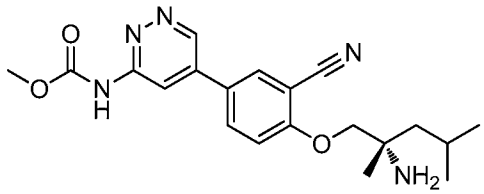
A mixture of 3,5-dichloropyridazine (1.5 g, 10.07 mmol), methyl carbamate (0.831 g, 11.08 mmol), XANTPHOS (0.466 g, 0.805 mmol), $PdOAc_2$ (0.226 g, 1.007 mmol) and Cs_2CO_3 (6.56 g, 20.14 mmol) were taken in 1,4-dioxane (40 mL) and heated at 85 °C overnight. The reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford methyl (5-chloropyridazin-3-yl)carbamate (1.71 g, 9.12 mmol, 91% yield) as a brown solid. LCMS (ESI) *m/e* 187.9 $[(M+H)^+$, calcd for $C_6H_7ClN_3O_2$ 188.0]; LC/MS retention time (Method C): t_R = 0.59 min.



Part B. Boc-(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate

A mixture of methyl (5-chloropyridazin-3-yl)carbamate (0.03 g, 0.160 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 (prepared as in Example 86, Parts A and B) (0.073 g, 0.160 mmol), KBr (0.019 g, 0.160 mmol), potassium phosphate, tribasic (0.056 g, 0.320 mmol) and $Pd(Ph_3P)_4$ (0.015 g, 0.013 mmol) were taken in 1,4-dioxane (1 mL) and heated at 100 °C overnight. After cooling, the reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford crude Boc-(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate (70 mg, 0.145 mmol, 90% yield) as a brown solid which was carried forward without further purification.

LCMS (ESI) *m/e* 484.2 [(M+H)$^+$, calcd for $C_{25}H_{34}N_5O_5$ 484.2]; LC/MS retention time (method B): t_R = 1.02 min.

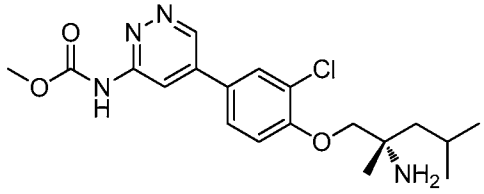


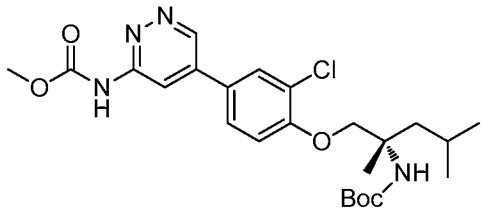
Part C. (S)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate

A solution of Boc-(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate (0.07 g, 0.145 mmol) in dichloromethane (1 mL) at 0 °C was treated with 4N hydrogen chloride in 1,4-dioxane (0.362 mL, 1.448 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, quenched with 10% aq. $NaHCO_3$ solution and ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyridazin-3-yl)carbamate (3.5 mg, 8.67 μmol, 6% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 384.2 [(M+H)$^+$, calcd for $C_{20}H_{26}N_5O_3$ 384.2]; LC/MS retention time (method B): t_R = 0.65 min; LC/MS retention time (method D): t_R = 1.17 min; LC/MS retention time (Method E): t_R = 0.93 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.22 (s, 1H), 8.53 (s, 1H), 8.24 (s, 1H), 8.12 - 8.16 (m, 1H), 7.44-7.47 (d, *J* = 8.8 Hz, 1H), 4.21-4.24 (s, 2H), 3.86 (s, 3H), 1.81-1.90 (m, 2H), 1.65 -1.71 (m, 1H), 1.46 (s, 3H), 1.02-1.09 (m, 6H) ppm.

Example 301

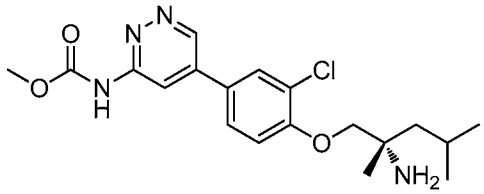
(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate





Part A. Boc-(S)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate

A mixture of methyl (5-chloropyridazin-3-yl)carbamate (prepared as described in Example 300) (0.05 g, 0.267 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.137 g, 0.293 mmol) (prepared as described in Example 285, Part A), Cs_2CO_3 (0.174 g, 0.533 mmol) and $PdCl_2$(dppf) (9.75 mg, 0.013 mmol) were taken in 1,4-dioxane (3 mL)-water (0.5 mL) and heated at 90 °C for 5h. After cooling, the reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford crude Boc-(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate (120 mg, 0.243 mmol, 92% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 493.2 [$(M+H)^+$, calcd for $C_{24}H_{34}ClN_4O_5$ 493.2]; LC/MS retention time (method B): t_R = 1.11 min.



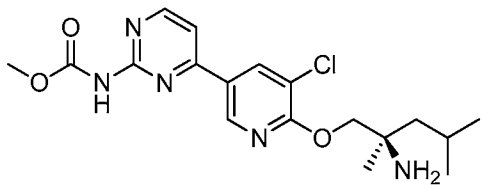
Part B. (S)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate

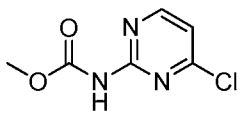
A solution of Boc-(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)-pyridazin-3-yl)carbamate (0.12 g, 0.243 mmol) in dichloromethane (2 mL) was treated with 4N hydrogen chloride in 1,4-dioxane (0.61 mL, 2.43 mmol). The mixture was stirred at room temperature for 1.5 h. The reaction mixture was concentrated, diluted with 10% aq. $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and

concentrated to afford (*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate (6 mg, 0.015 mmol, 6% yield) as a brown solid. LCMS (ESI) *m/e* 393.1 [(M+H)$^+$, calcd for $C_{19}H_{26}ClN_4O_3$ 393.2]; LC/MS retention time (method B): t_R = 0.69 min; LC/MS retention time (method D): t_R = 1.22 min; LC/MS retention time (Method E): t_R = 1.10 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.17 (d, *J* = 2.4 Hz, 1H), 8.49 (d, *J* = 2.0 Hz, 1H), 7.95 (d, *J* = 2.4 Hz, 1H), 7.79-7.82 (m, 1H), 7.34-7.36 (d, *J* = 8.8 Hz, 1H), 4.18-4.27 (m, 2H), 3.84 (s, 3H), 1.85-1.96 (m, 2H), 1.68 -1.74 (m, 1H), 1.53 (s, 3H), 1.02-1.09 (m, 6H) ppm.

Example 304

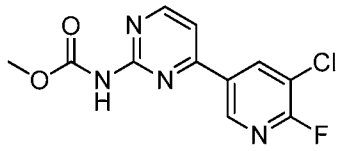
(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate





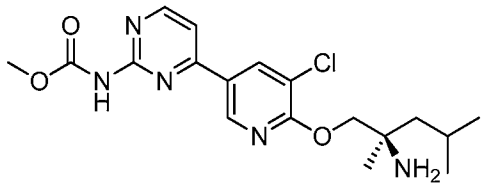
Part A: methyl (4-chloropyrimidin-2-yl)carbamate

To a stirred solution of 4-chloropyrimidin-2-amine (1 g, 7.72 mmol) in THF (20 mL) at 0 °C was added potassium *tert*-butoxide (2.60 g, 23.16 mmol) and stirred for 30 min. To this mixture was added methyl chloroformate (1.495 mL, 19.30 mmol) dropwise and the mixture stirred for another 16 h at room temperature. The reaction mixture was quenched with 10% aq. sodium bicarbonate solution (30 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na_2SO_4, and concentrated under reduced pressure to afford methyl (4-chloropyrimidin-2-yl)carbamate (900 mg, 4.51 mmol, 58% yield) as a yellow solid. LCMS (ESI) *m/e* 188.0 [(M+H)$^+$, calcd for $C_6H_7ClN_3O_2$ 188.0]; LC/MS retention time (Method C): t_R = 0.50 min.



Part B: Methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (75 mg, 0.400 mmol), (5-chloro-6-fluoropyridin-3-yl)boronic acid (70.1 mg, 0.400 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (16.33 mg, 0.020 mmol) and Cs_2CO_3 (391 mg, 1.199 mmol) in 1,4-dioxane (2.5 mL)-water (02 mL) was purged with nitrogen and heated at 100 °C for 12 h. The solution cooled to room temperature and was concentrated under reduced pressure. Water (50 mL) was added and the solution was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc in hexanes) to afford methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (55 mg, 0.144 mmol, 36% yield) as a brown solid. LCMS (ESI) *m/e* 283.0 [$(M+H)^+$, calcd for $C_{11}H_9ClFN_4O_2$ 283.0]; LC/MS retention time (Method A1): t_R = 2.01 min.



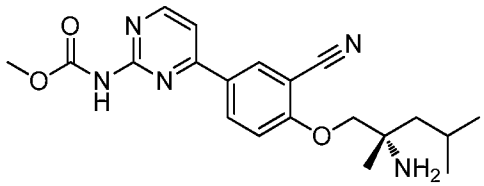
Part C: (R)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate

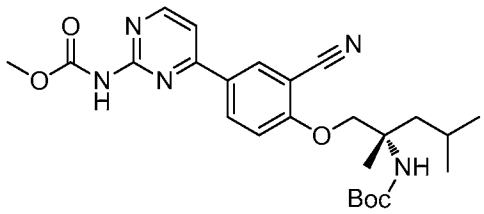
To a stirred solution of (*R*)-2-amino-2,4-dimethylpentan-1-ol (23.21 mg, 0.177 mmol) in DMF (2.5 mL) at 0 °C was added NaH (14.15 mg, 0.354 mmol) followed by methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (50 mg, 0.177 mmol) in 0.5 mL DMF. The mixture was heated at 60 °C for 12 h. The mixture was then was cooled to 0 °C, diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*R*)-methyl (4-(6-((2-

amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate (3 mg, 0.724 mmol, 4% yield). LCMS (ESI) *m/e* 394.2 [(M+H)$^+$, calcd for $C_{18}H_{25}ClN_5O_3$ 394.2]; LC/MS retention time (Method A1): t_R = 1.23 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.94 (d, *J*=2.13 Hz, 1H), 8.68 (d, *J*=2.13 Hz, 1H), 8.64 (d, *J*=5.27 Hz, 1H), 7.65 (d, *J*=5.33 Hz, 1H), 4.61 (d, *J*=3.14 Hz, 2H), 3.84 (s, 3H), 1.87 - 1.96 (m, 2H), 1.68 - 1.75 (m, 1H), 1.54 (s, 3H), 1.08 (m, 6H) ppm.

Example 305

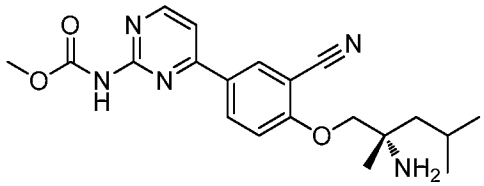
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate





Part A. Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.267 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 (prepared as in Example 86, Parts A and B) (0.122 g, 0.267 mmol), $PdCl_2$(dppf) (0.016 g, 0.021 mmol) and Cs_2CO_3 (0.174 g, 0.533 mmol) were taken in 1,4-dioxane (2 mL)-water (0.5 mL). The mixture was stirred at 80 °C overnight. The reaction mixture was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate (110 mg, 85%) as brownish solid. LCMS (ESI) *m/e* 484.3 [(M+H)$^+$, calcd for $C_{25}H_{34}N_5O_5$ 484.2]; LC/MS retention time (method B): t_R = 1.02 min.

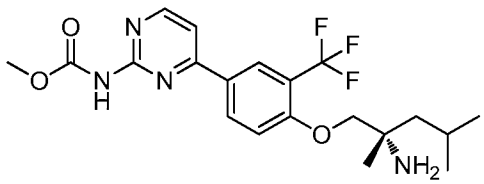


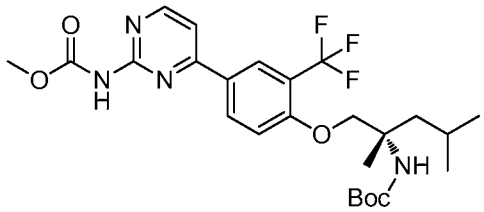
Part B. (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate (0.1 g, 0.207 mmol) was treated with 4N hydrogen chloride in 1,4-dioxane (0.517 mL, 2.068 mmol) for 4 h. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-cyanophenyl)pyrimidin-2-yl)carbamate (5 mg, 0.013 mmol, 6% yield) as a white solid. LCMS (ESI) *m/e* 384.2 [$(M+H)^+$, calcd for $C_{20}H_{26}N_5O_3$ 384.2]; LC/MS retention time (method A2): t_R = 1.64 min. HPLC retention time (method A): t_R = 5.47 min; HPLC retention time (method B): t_R = 5.93 min. ^1H NMR (400 MHz, *METHANOL-d4*): δ 8.59 (d, *J* = 5.2 Hz, 1H), 8.56 (d, *J* = 2.0 Hz, 1H), 8.46-8.49 (m, 1H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 4.09 (m, 2H), 3.82 (s, 3H), 1.82-1.88 (m, 1H), 1.56 -1.72 (m, 2H), 1.34 (s, 3H), 0.98-1.08 (m, 6H) ppm.

Example 306

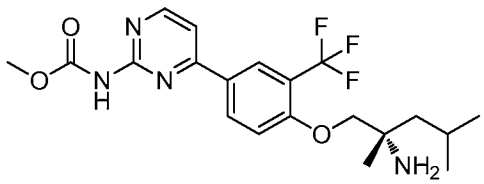
(*S*)-methyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate





Part A. Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.267 mmol), (*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 215, Parts A and B) (0.147 g, 0.293 mmol), Cs_2CO_3 (0.261 g, 0.800 mmol) and $PdCl_2$(dppf) (9.75 mg, 0.013 mmol) were taken in 1,4-dioxane (2 mL)-water (0.5 mL). The mixture was heated at 80 C overnight. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (150 mg, quant. yield) as a brownish solid. LCMS (ESI) *m/e* 527.3 $[(M+H)^+$, calcd for $C_{25}H_{34}F_3N_4O_5$ 527.2]; LC/MS retention time (method B): t_R = 1.13 min.



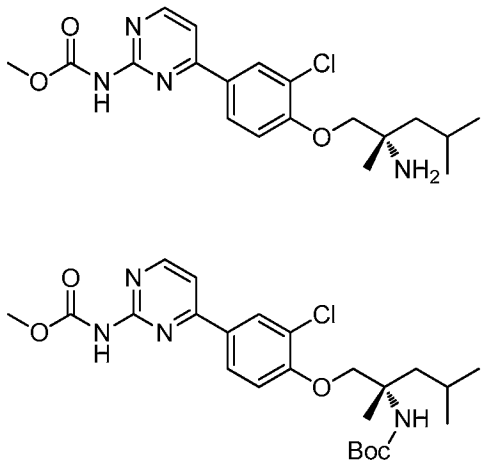
Part B. (S)-methyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-methyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (150 mg, 0.285 mmol) was treated with 4N hydrogen chloride (0.712 mL, 2.85 mmol) at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-methyl (4-

(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (35 mg, 0.080 mmol, 28% yield) as a pale yellow solid. LCMS (ESI) *m/e* 427.3 [$(M+H)^+$, calcd for $C_{20}H_{26}F_3N_4O_3$ 427.2]; LC/MS retention time (method B): t_R = 0.70 min; LC/MS retention time (method D): t_R = 1.52 min; LC/MS retention time (Method E): t_R = 1.11 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.59 (d, *J* = 5.2 Hz, 1H), 8.52 (s, 1H), 8.41-8.44 (m, 1H), 7.61(d, *J* = 5.6 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 4.04-4.12 (m, 2H), 3.81 (s, 3H), 1.81-1.86 (m, 1H), 1.55 -1.81 (m, 2H), 1.39 (s, 3H), 1.01-1.08 (m, 6H) ppm.

Example 307

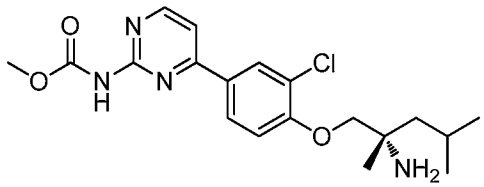
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate



Part A. Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.267 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 285, Part A) (0.137 g, 0.293 mmol), Cs_2CO_3 (0.261 g, 0.800 mmol) and $PdCl_2$(dppf) (9.75 mg, 0.013 mmol) were taken in 1,4-dioxane (2 mL)-water (0.5 mL). The mixture was heated at 80 °C overnight. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate

(136 mg, quant. yield) as a brownish solid. LCMS (ESI) *m/e* 493.2 [$(M+H)^+$, calcd for $C_{24}H_{34}ClN_4O_5$ 493.2]; LC/MS retention time (method B): t_R = 1.09 min.

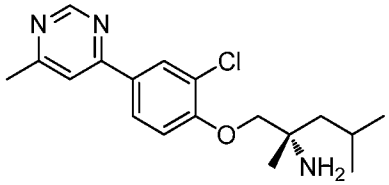


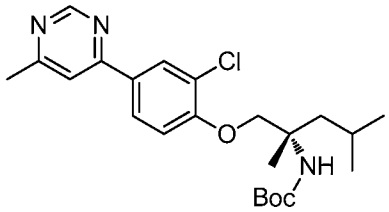
Part B. (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate (136 mg, 0.276 mmol) was treated with 4N hydrogen chloride (0.690 mL, 2.76 mmol) overnight. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-methyl (4-(4-((2-amino-2,4 dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate (24 mg, 0.057 mmol, 21% yield) as a pale yellow solid. LCMS (ESI) *m/e* 393.2 [$(M+H)^+$, calcd for $C_{19}H_{26}ClN_4O_3$ 393.2]; LC/MS retention time (method B): t_R = 0.66 min; LC/MS retention time (method D): t_R = 1.29 min; LC/MS retention time (Method E): t_R = 1.04 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.47 (d, J = 5.2 Hz, 1H), 8.22 (s, 1H), 8.02-8.05 (m, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 3.95-4.02 (m, 2H), 3.71 (s, 3H), 1.65-1.77 (m, 2H), 1.50 - 1.55 (m, 1H), 1.31 (s, 3H), 0.85-1.01 (m, 6H) ppm.

Example 308

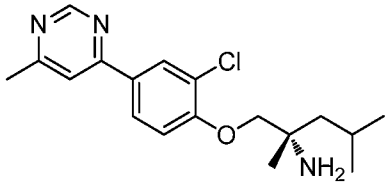
(*S*)-1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





Part A. (S)-tert-butyl (1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-6-methylpyrimidine (0.05 g, 0.389 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 285, Part A) (0.182 g, 0.389 mmol), Cs_2CO_3 (0.253 g, 0.778 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) were taken in 1,4-dioxane (3 mL)-water (0.3 mL). The mixture was heated at 90 °C for 3h. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na2SO4, filtered, and concentrated to afford (*S*)-*tert*-butyl (1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (120 mg, 0.277 mmol, 71% yield) as a brownish solid. LCMS (ESI) *m/e* 434.2 [$(M+H)^+$, calcd for $C_{23}H_{33}ClN_3O_3$ 434.2]; LC/MS retention time (method B): t_R = 1.13 min.



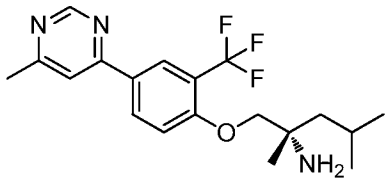
Part B. (S)-1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

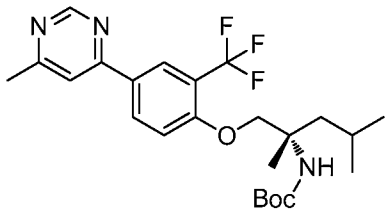
A solution of (*S*)-*tert*-butyl (1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.12 g, 0.277 mmol) in DCM (2 mL) was treated with 4N hydrogen chloride in 1,4-dioxane (0.691 mL, 2.77 mmol) overnight. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (16 mg, 0.047 mmol, 17% yield) as a brown solid. LCMS (ESI) *m/e* 334.1 [$(M+H)^+$, calcd

for $C_{18}H_{25}ClN_3O$ 334.2]; LC/MS retention time (method B): t_R = 0.81 min; LC/MS retention time (method D): t_R = 1.50 min; LC/MS retention time (Method E): t_R = 1.16 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.04 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 2.0, 1H), 8.16-8.19 (m, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 3.82-3.88 (m, 2H), 1.89 (s, 3H), 1.79-1.86 (m, 1H), 1.36-1.43 (m, 2H), 1.14 (s, 3H), 0.90-0.98 (m, 6H) ppm.

Example 309

(*S*)-2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

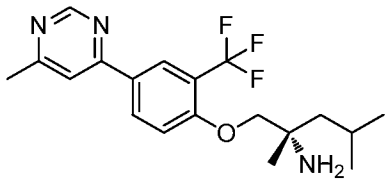




Part A. (S)-tert-butyl(2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2 (trifluoromethyl)phenoxy)pentan-2-yl)carbamate

A mixture of 4-chloro-6-methylpyrimidine (0.05 g, 0.389 mmol), (*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 215) (0.195 g, 0.389 mmol), Cs_2CO_3 (0.253 g, 0.778 mmol) and $PdCl_2$(dppf) (0.014 g, 0.019 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was heated at 80 °C overnight. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-*tert*-butyl(2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2 (trifluoromethyl)phenoxy)pentan-2-yl)carbamate (98 mg, 0.210 mmol, 54% yield) as a brownish solid. LCMS (ESI) *m/e*

468.2 [(M+H)$^+$, calcd for $C_{24}H_{33}F_3N_3O_3$, 468.2]; LC/MS retention time (Method A1): t_R = 2.87 min.

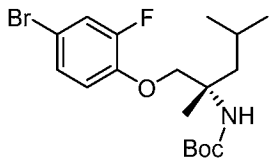


Part B. (S)-2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

(*S*)-*tert*-Butyl (2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2 (trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.12 g, 0.257 mmol) was treated with 4N hydrogen chloride in 1,4-dioxane (0.642 mL, 2.57 mmol) for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-2,4 dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine (6 mg, 0.015 mmol, 6% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.1 [(M+H)$^+$, calcd for $C_{19}H_{25}F_3N_3O$, 368.2]; LC/MS retention time (method B): t_R = 0.96 min; LC/MS retention time (method D): t_R = 1.71 min; LC/MS retention time (Method E): t_R = 1.26 min. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 9.08 (d, J = 0.8 Hz, 1H), 8.47-8.51 (m, 2H), 8.08 (d, J = 0.8 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 3.96-4.02 (m, 2H), 2.54 (s, 3H), 1.78-1.86 (m, 1H), 1.41 -1.52 (m, 2H), 1.20 (s, 3H), 0.92-0.98 (m, 6H) ppm.

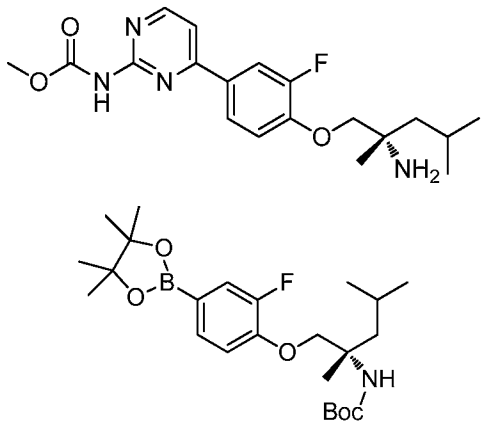
Example 310

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



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

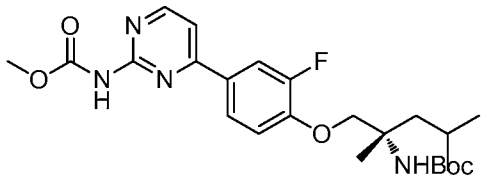
A solution of 4-bromo-2-fluorophenol (1.2 g, 6.28 mmol), K2CO3 (2.60 g, 18.85 mmol), and (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (2.212 g, 7.54 mmol) in DMF (20 mL) was heated to 80° C for 16 h. The reaction mixture was allowed to cool to room temperature, the volatiles were evaporated to dryness under reduced pressure, water (10 mL) was added and the mixture extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with 10 % aq. sodium hydroxide solution (10 mL) then water (20 mL). The organic layer was dried over sodium sulphate, filtered and volatiles were evaporated to dryness under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-bromo-2-fluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (210 mg, 0.519 mmol, 83 % yield) as pale brown oil which was carried forward without further purification. ^{1}H NMR (400MHz, CHLOROFORM-d) δ 7.24 (dd, *J*=10.4, 2.4 Hz, 1H), 7.20 - 7.14 (m, 1H), 6.89 (t, *J*=8.8 Hz, 1H), 4.58 (br. s., 1H), 4.18 (d, *J*=9.0 Hz, 1H), 4.00 (d, *J*=9.0 Hz, 1H), 1.95 - 1.73 (m, 2H), 1.58 - 1.50 (m, 1H), 1.39 (s, 3H), 1.00 (d, *J*=2.8 Hz, 3H), 0.98 (d, *J*=2.8 Hz, 3H).



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

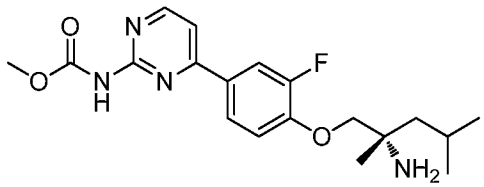
A mixture of (*S*)-*tert*-butyl (1-(4-bromo-2-fluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (1.751 g, 4.33 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.1 g, 4.33 mmol), and potassium acetate (0.850 g, 8.66 mmol) in 1,4-dioxane (20 mL) was heated at 90 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water and ethyl acetate. The ethyl acetate layer was

collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford a yellowish semi-solid. The residue was purified by silica gel chromatography (5-10% EtOAc-hexane) to obtain (*S*)-*tert*-butyl (1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate as colorless oil (1.7 g, 3.77 mmol, 87% yield). LCMS (ESI) *m/e* 352.2 [(M+H-Boc)$^+$, calcd for $C_{24}H_{40}BFNO_5$ 452.2]; LC/MS retention time (method B): t_R = 1.33 min. De-Boc mass was detected by LCMS. ^{1}H NMR (400 MHz, *CDCl$_3$*) : δ 7.45-7.49 (m, 2H), 6.94-6.98 (m, 1H), 4.60 (bs, NH, 1H), 4.16 (m, 1H), 4.00 (m, 1H), 1.82 (m, 2H), 1.60 (m, 1H), 1.59 (s, 3H), 1.39 (s, 9H), 1.24 (s, 12H), 0.92-0.99 (m, 6H) ppm.



Part C. Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.267 mmol), (*S*)-*tert*-butyl (1-(2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.120 g, 0.267 mmol), Cs_2CO_3 (0.174 g, 0.533 mmol) and $PdCl_2$(dppf) (9.75 mg, 0.013 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was heated at 90 °C for 6h. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyrimidin-2-yl)carbamate (160 mg, quant. yield) as a brownish solid. LCMS (ESI) *m/e* 477.3 [(M+H)$^+$, calcd for $C_{24}H_{34}FN_4O_5$ 477.2]; LC/MS retention time (method B): t_R = 1.09 min.

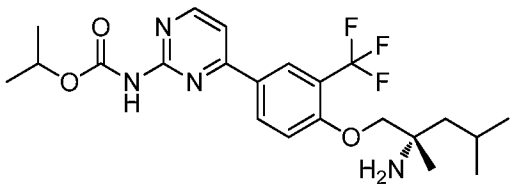


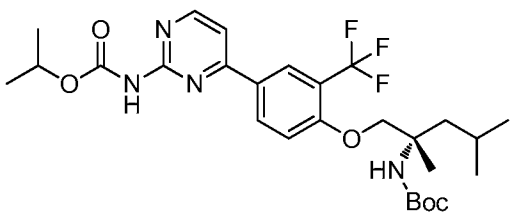
Part D. (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyrimidin-2-yl)carbamate (160 mg, 0.336 mmol) was treated with 4N hydrogen chloride (1.679 mL, 3.36 mmol) for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)pyrimidin-2-yl)carbamate (11 mg, 0.029 mmol, 9% yield) as a pale yellow solid. LCMS (ESI) *m/e* 377.1 [$(M+H)^+$, calcd for $C_{19}H_{26}FN_4O_3$ 377.2]; LC/MS retention time (method B): t_R = 0.66 min; LC/MS retention time (method D): t_R = 1.81 min; LC/MS retention time (Method E): t_R = 1.58 min. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 10.46 (s, *NH*, 1H), 8.65 (d, *J* = 5.3 Hz, 1H), 8.13-8.17 (m, 2H), 8.10 (bs, NH2, 2H), 7.72 (d, *J* = 5.4 Hz, 1H), 7.39-7.44 (m, 1H), 4.14-4.21 (m, 2H), 3.69 (s, 3H), 1.79-1.83 (m, 1H), 1.69-1.75 (m, 1H), 1.56-1.58 (m, 1H), 1.37 (s, 3H), 0.92-0.98 (m, 6H) ppm.

Example 311

(*S*)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

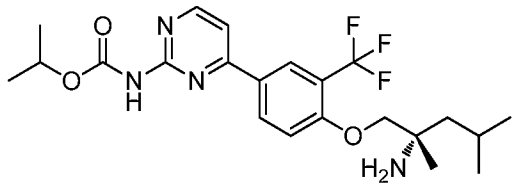




Part A. Boc-(S)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

A mixture of isopropyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.232 mmol), (*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 215, Parts A and B) (0.116 g, 0.232 mmol), Cs_2CO_3 (0.151 g, 0.464 mmol) and $PdCl_2$(dppf) (8.48 mg, 0.012 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was heated at 90 °C overnight. It was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na2SO4, filtered, and concentrated to afford Boc-(*S*)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (84 mg, 0.151 mmol, 65% yield) as a brownish solid. LCMS (ESI) *m/e* 555.7 [$(M+H)^+$, calcd for $C_{27}H_{38}F_3N_4O_5$ 555.6]; LC/MS retention time (method B): t_R = 1.20 min.

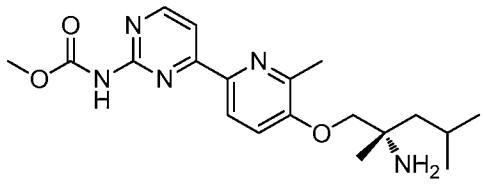


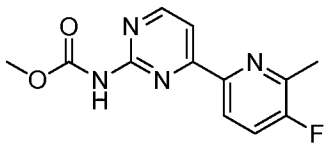
Part B. (S)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (84 mg, 0.151 mmol) was treated with 2N hydrogen chloride in 1,4-dioxane (0.757 mL, 1.515 mmol) for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded off-white solid as crude product. The crude material was purified by prep LC/MS (method A) to afford (*S*)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (16 mg, 0.033 mmol, 22% yield) as a pale yellow solid. LCMS (ESI) *m/e* 455.2 [$(M+H)^+$, calcd for $C_{22}H_{30}F_3N_4O_3$ 455.2]; LC/MS retention time (method B): t_R = 0.84 min; LC/MS retention time (method D): t_R = 2.61 min; LC/MS retention time (Method E): t_R = 1.97 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 8.59 (d, *J* = 5.2 Hz, 1H), 8.51 (d, *J* = 2.0 Hz, 1H), 8.41-8.45 (m, 1H), 7.61 (d, *J* = 5.2 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 5.03-5.10 (m, 1H), 3.98-4.05 (m, 2H), 1.80-1.87 (m, 1H), 1.50-1.64 (m, 2H), 1.35-1.37 (m, 6H), 1.29 (s, 3H), 0.98-1.02 (m, 6H) ppm. ^{19}F NMR (400 MHz, *CD_3OD*): δ -63.58 ppm.

Example 312

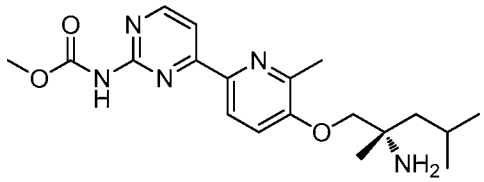
(*S*)-methyl (4-(5-((2-amino-2,4 dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate





Part A. Methyl (4-(5-fluoro-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate

A solution of 6-bromo-3-fluoro-2-methylpyridine (0.1 g, 0.526 mmol) in THF (1 mL) at -78 °C was treated with n-BuLi (0.289 mL, 0.579 mmol). The mixture was stirred for 1 h at -78 °C and then zinc bromide (0.178 g, 0.789 mmol) was added. The mixture was stirred another 30 min at -78 °C, then it was removed from the cooling bath and stirred at room temperature for 1 h. To the resulting mixture was slowly added a solution of $Pd_2(dba)_3$ (0.024 g, 0.026 mmol), 2-dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl (0.020 g, 0.042 mmol) and methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.099 g, 0.526 mmol) in THF (0.5 mL). The reaction mixture was heated at 70 °C overnight. It was quenched with 10% aq. $NaHCO_3$ and diluted with ethyl acetate (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated to afford methyl (4-(5-fluoro-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate (0.124 g, 0.473 mmol, 90% yield) as a brown solid. LCMS (ESI) *m/e* 263.0 $[(M+H)^+$, calcd for $C_{12}H_{12}FN_4O_2$ 263.2]; LC/MS retention time (method B): t_R = 0.79 min. ^1H NMR (400 MHz, *DMSO-d6*): δ 10.55 (s, *NH*, 1H), 8.75 (d, J = 5.2 Hz, 1H), 8.32-8.36 (m, 1H), 7.91 (d, J = 5.2 Hz, 1H), 7.85-7.90 (m, 1H), 3.71 (s, 3H), 2.51 (s, 3H) ppm. ^{19}F NMR (400 MHz, *CDCl3*): δ -121.22 ppm.

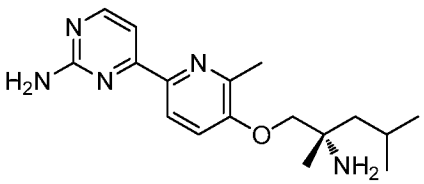


Part B. (S)-methyl (4-(5-((2-amino-2,4 dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate

(*S*)-2-Amino-2,4-dimethylpentan-1-ol (0.015 g, 0.114 mmol) was dissolved in THF (2 mL), cooled to 0 °C and sodium hydride (7.32 mg, 0.305 mmol) was added. To the resulting mixture was slowly added a solution of methyl (4-(5-fluoro-6 methylpyridin-2-yl)pyrimidin-2-yl)carbamate (0.02 g, 0.076 mmol) in THF (1 mL). The mixture was stirred at 60 °C overnight. The reaction mixture was cooled to room temperature then was quenched with ice-water, diluted with brine and ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-methyl (4-(5-((2-amino-2,4 dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate (1 mg, 2.62 μmol, 4% yield) as a pale yellow solid. LCMS (ESI) *m/e* 374.2 $[(M+H)^+$, calcd for $C_{19}H_{28}N_5O_3$ 374.2]; LC/MS retention time (Method A1): t_R = 2.02 min; LC/MS retention time (method D): t_R = 1.79 min; LC/MS retention time (Method E): t_R = 1.47 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 8.62 (d, *J* = 5.2 Hz, 1H), 8.38 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 4.14-4.24 (m, 2H), 3.82 (s, 3H), 2.62 (s, 3H), 1.85-1.92 (m, 2H), 1.69-1.73 (m, 1H), 1.53 (s, 3H), 0.90-1.10 (m, 6H) ppm.

Example 313

(*S*)-4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-amine

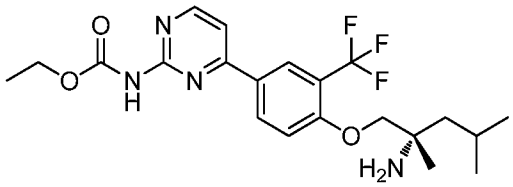


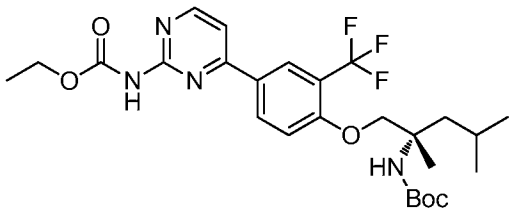
Prepared as described in Example 312. The final reaction also afforded carbamate cleaved product, (*S*)-4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-amine (7 mg, 0.022 mmol, 28% yield) as a pale yellow solid. LCMS (ESI) *m/e* 316.2 $[(M+H)^+$, calcd for $C_{17}H_{26}N_5O$, 316.2]; LC/MS retention time (Method A1): t_R = 1.96 min; LC/MS retention time (method D): t_R =

1.66 min; LC/MS retention time (Method E): t_R = 1.29 min. ^{1}H NMR (400 MHz, *CD$_3$OD*): δ 8.33 (d, *J* = 5.6 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 5.6 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 4.14-4.24 (m, 2H), 2.62 (s, 3H), 1.87-1.91 (m, 2H), 1.70-1.73 (m, 1H), 1.53 (s, 3H), 0.90-1.09 (m, 6H) ppm.

Example 314

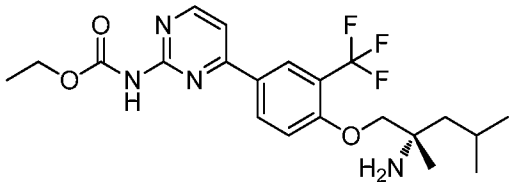
(*S*)-ethyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate





Part A. Boc-(S)-ethyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

A mixture of ethyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.248 mmol), (*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 215, Parts A and B) (0.124 g, 0.248 mmol), Cs_2CO_3 (0.162 g, 0.496 mmol) and $PdCl_2$(dppf) (9.07 mg, 0.012 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was heated at 90 °C overnight. It was concentrated, diluted with brine and ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford Boc-(*S*)-ethyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (80 mg, 0.148 mmol, 60% yield) as brownish solid. LCMS (ESI) *m/e* 541.2 [(M+H)$^+$, calcd for $C_{26}H_{36}F_3N_4O_5$ 541.2]; LC/MS retention time (method B): t_R = 1.18 min.

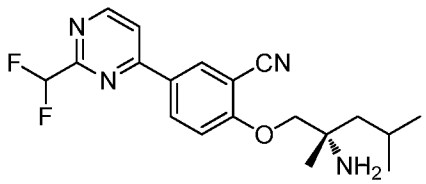


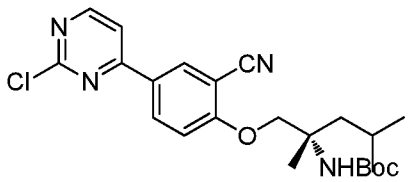
Part B. (S)-ethyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate

Boc-(*S*)-ethyl(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (80 mg, 0.148 mmol) was treated with 2N hydrogen chloride in 1,4-dioxane (0.740 mL, 1.480 mmol) for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with aq. $NaHCO_3$ solution and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-ethyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate (13 mg, 0.029 mmol, 20% yield) as a pale yellow solid. LCMS (ESI) *m/e* 441.2 $[(M+H)^+$, calcd for $C_{21}H_{28}F_3N_4O_3$ 441.2]; LC/MS retention time (method B): t_R = 0.80 min; LC/MS retention time (method D): t_R = 2.43 min; LC/MS retention time (Method E): t_R = 2.04 min. ^{1}H NMR (400 MHz, *DMSO-d6*): δ 10.4 (s, *NH*, 1H), 8.68 (d, *J* = 5.2 Hz, 1H), 8.56-8.50 (m, 2H), 8.05 (bs, *NH*, 2H), 7.79 (d, *J* = 5.6 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 4.24-4.14 (m, 4H), 1.83-1.80 (m, 1H), 1.76-1.70 (m, 1H),1.64-1.60 (m, 1H), 1.39 (s, 3H), 1.29-1.25 (m, 3H), 0.99-0.90 (m, 6H) ppm. ^{19}F NMR (400 MHz, *CD3OD*): δ -63.34 and -63.54 ppm.

Example 315

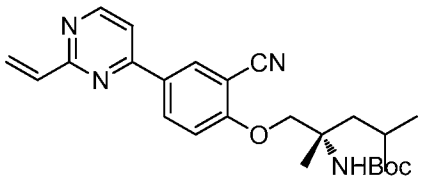
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyrimidin-4-yl)benzonitrile





Part A. (S)-tert-Butyl (1-(4-(2-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate

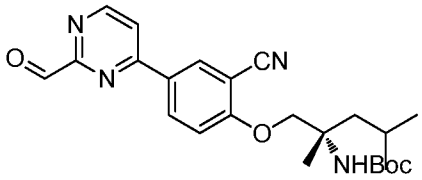
A suspension of 2,4-dichloropyrimidine (1.3 g, 8.73 mmol), (*S*)-*tert*-butyl (1-(2-cyano-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as in Example 86, Parts A and B) (4.00 g, 8.73 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.356 g, 0.436 mmol) and potassium phosphate tribasic (4.01 g, 26.2 mmol) in 1,4-dioxane (30 mL) and water (1 mL) was purged with nitrogen and heated to 90 °C for 5 h. The reaction mixture was diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (pet ether:ethyl acetate) to afford (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (3.2 g, 5.90 mmol, 67.6 % yield) as a brown semi-solid. LCMS (ESI) *m/e* 445.2 $[(M+H)^+$, calcd for $C_{23}H_{30}ClN_4O_3$ 445.2]; LC/MS retention time (Method G): t_R = 3.86 min.



Part B. (S)-tert-butyl (1-(2-cyano-4-(2-vinylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate.

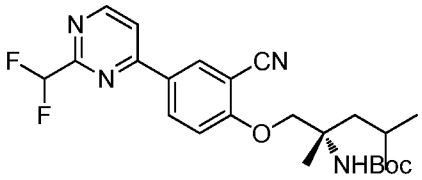
A solution of (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (3.2 g, 7.19 mmol), 2,4,6-trivinylcyclotriboroxane pyridine complex (1.904 g, 7.91 mmol), Cs_2CO_3 (7.03 g, 21.58 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.294 g, 0.360 mmol) in 1,4-dioxane (50 mL) and water (1 mL) was purged with nitrogen and heated to 90 °C for 5 h. The reaction mixture was diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl

acetate (50 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (pet ether:ethyl acetate) to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(2-vinylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (2.4 g, 4.51 mmol, 63% yield) as a brown semi-solid. LCMS (ESI) *m/e* 437.3 [$(M+H)^+$, calcd for $C_{25}H_{33}N_4O_3$ 437.2]; LC/MS retention time (Method C): t_R = 1.27 min.



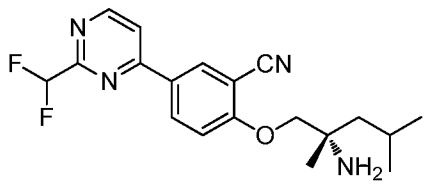
Part C. (S)-tert-butyl (1-(2-cyano-4-(2-formylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-vinylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (1 g, 2.291 mmol) in 1,4-dioxane (30 mL) and water (10 mL) at 0 °C, was added 2,6-lutidine (0.400 mL, 3.44 mmol) and 2.5% osmium tetroxide in *tert*-butanol (0.863 mL, 0.069 mmol). The reaction mixture was stirred for 10 min at 0 °C and sodium periodate (1.960 g, 9.16 mmol) was added. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL), and saturated NaCl (1 x 20 mL). The organic was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via silica gel chromatography (petroleum ether:ethyl acetate) to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(2-formylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (450 mg, 0.954 mmol, 41.7 % yield) as a brown semi-solid. LCMS (ESI) *m/e* 439.2 [$(M+H)^+$, calcd for $C_{24}H_{31}N_4O_4$, 439.2]; LC/MS retention time (Method G): t_R = 2.79 min.



Part D. (S)-tert-butyl (1-(2-cyano-4-(2-(difluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-formylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (450 mg, 1.026 mmol) in dichloromethane (20 mL) at -70 °C, was added DAST (0.271 mL, 2.052 mmol). The reaction mixture was slowly allowed to warm to -30°C, stirred for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane(2 x 50 mL). The dichloromethane layer was washed with water (1 x 20 mL) and saturated NaCl (1 x 20 mL). The organic was dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (petroleum ether:ethyl acetate) to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(2-(difluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (150 mg, 0.322 mmol, 31% yield) as a pale yellow semi-solid. LCMS (ESI) *m/e* 461.2 [$(M+H)^+$, calcd for $C_{24}H_{31}F_2N_4O_3$, 461.2]; LC/MS retention time (Method G): t_R = 3.71 min.



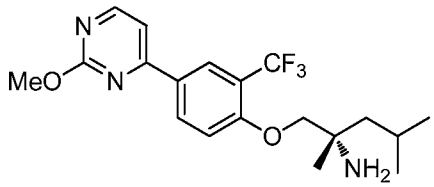
Part E. (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyrimidin-4-yl)benzonitrile.

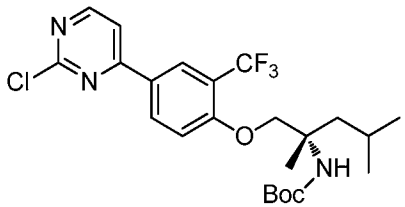
To a solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-(difluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (150 mg, 0.326 mmol) in dichloromethane (3 mL) at 0 °C, was added 2 M HCl in diethyl ether (8.14 mL, 16.29 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was cooled to 0 °C, quenched with saturated sodium bicarbonate solution (25 mL) and extracted with dichloromethane (2 x 50 mL). The dichloromethane layer was washed with water (1 x 20 mL), and saturated NaCl (1 x 20 mL). The organic was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The yellow gummy solid was triturated with diethyl ether (2 x 10 mL) to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(difluoromethyl)pyrimidin-4-yl)benzonitrile (65 mg, 0.173 mmol, 53% yield) as a yellow solid. LCMS (ESI) *m/e* 361.2 [$(M+H)^+$,

calcd for $C_{19}H_{23}F_2N_4O$, 361.2]; LC/MS retention time (Method G): t_R = 2.66 min. ^1H NMR (400 MHz, Methanol-*d4*): δ 8.96 (d, *J*=5.3 Hz, 1H), 8.58 - 8.69 (m, 2H), 8.14 (d, *J*=5.27 Hz, 1H), 7.48 (d, *J*=8.72 Hz, 1H), 6.64 - 6.96 (m, 1H), 4.36 (s, 2H), 1.85 - 2.02 (m, 2H), 1.74 (dd, *J* = 13.80, 4.89 Hz, 1H), 1.56 (s, 3H) 1.08 (m, 6H) ppm.

Example 316

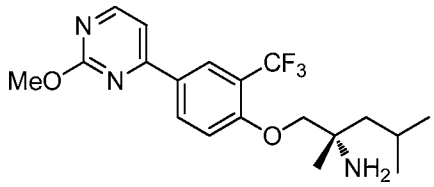
(*S*)-1-(4-(2-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine





Part A. (S)-tert-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A solution of 2,4-dichloropyrimidine (0.05 g, 0.336 mmol), (*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 215, Parts A and B) (0.168 g, 0.336 mmol), Cs_2CO_3 (0.219 g, 0.671 mmol) and $PdCl_2$(dppf) (0.012 g, 0.017 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was heated at 90 °C overnight. The reaction mixture was concentrated, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated which afforded brownish solid . The crude product was washed with hexane (5 x 2 mL) and dried under vacuum to afford (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate(176 mg, quant. yield). LCMS (ESI) *m/e* 488.6 $[(M+H)^+$, calcd for $C_{23}H_{30}ClF_3N_3O_3$ 488.2]; LC/MS retention time (method B): t_R = 1.35 min.

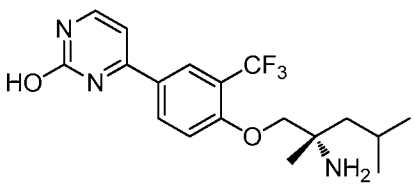


Part B. (S)-1-(4-(2-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

In a 50 mL round-bottomed flask, (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.102 mmol) was taken in methanol (2 mL). Hydrochloric acid in methanol (0.256 mL, 1.025 mmol) was added and stirred at room temperature for 18 h. It was quenched with 10% $NaHCO_3$ and diluted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-1-(4-(2-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (2 mg, 4.69 μmol, 5% yield) as a pale yellow solid. LCMS (ESI) *m/e* 384.3 $[(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O_2$ 384.2]; LC/MS retention time (method H): t_R = 1.87 min; LC/MS retention time (method I): t_R = 1.31 min. ^1H NMR (400 MHz, methanol-d_4): δ 8.60 (d, *J* = 5.2 Hz, 1H), 8.45-8.51 (m, 2H), 7.62 (d, *J* = 5.2 Hz, 1H), 7.37-7.43 (m, 1H), 4.12-4.26 (m, 2H), 3.63 (s, 3H), 1.78-1.90 (m, 2H), 1.65-1.71 (m, 1H), 1.48 (s, 3H), 0.98-1.12 (m, 6H) ppm.

Example 317

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-ol

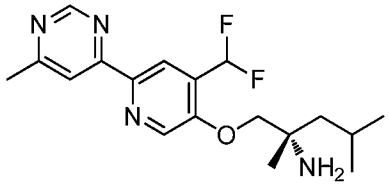


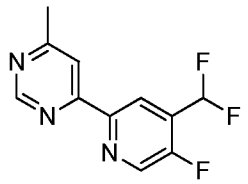
(*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 316) (0.05 g, 0.102 mmol) was taken in aq. 5N hydrogen chloride (2.049 mL, 10.25 mmol) and heated at 100 °C overnight. The reaction mixture was quenched with 10% $NaHCO_3$ and diluted with ethyl acetate (20 mL). The organic layer was separated, dried over

Na_2SO_4, filtered, and concentrated to afford (*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-ol (35 mg, 0.093 mmol, 91% yield) as a yellow solid. LCMS (ESI) *m/e* 370.2 $[(M+H)^+$, calcd for $C_{18}H_{23}F_3N_3O_2$, 370.2]; LC/MS retention time (method B): t_R = 0.69 min; LC/MS retention time (method D): t_R = 2.07 min; LC/MS retention time (Method E): t_R = 0.87 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 8.50 (d, *J* = 2.0 Hz, 1H), 8.43-8.46 (m, 1H), 8.03 (d, *J* = 5.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 5.8 Hz, 1H), 4.27-4.35 (m, 2H), 1.86-1.92 (m, 2H), 1.70-1.76 (m, 1H), 1.55 (s, 3H), 0.90-1.09 (m, 6H) ppm.

Example 318

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

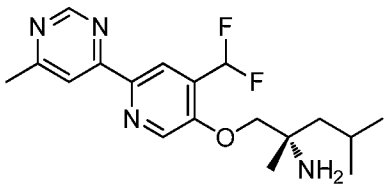




Part A. 4-(4-(difluoromethyl)-5-fluoropyridin-2-yl)-6-methylpyrimidine

A mixture of 4-chloro-6-methylpyrimidine (50 mg, 0.389 mmol), 2-bromo-4-(difluoromethyl)-5-fluoropyridine (88 mg, 0.389 mmol), 1,1,1,2,2,2-hexamethyldistannane (127 mg, 0.389 mmol) and $Pd(Ph_3P)_4$ (22.47 mg, 0.019 mmol) were heated at 160 °C in a microwave for 1 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford a brownish semi-solid. The crude material was purified by silica gel chromatography (20-30% EtOAc-hexane) to afford 4-(4-(difluoromethyl)-5-fluoropyridin-2-yl)-6-methylpyrimidine (25 mg, 0.073 mmol, 19% yield) as an off-white solid. LCMS (ESI) *m/e* 240.0 $[(M+H)^+$, calcd for

$C_{11}H_9F_3N_3$, 240.1]; LC/MS retention time (method B): t_R = 0.88 min and LC/MS retention time (method H): t_R = 2.04 min. ^{1}H NMR (300 MHz, *CDCl*$_3$): δ 9.17 (d, *J* = 1.2 Hz, 1H), 8.75 (d, *J* = 6.4 Hz, 1H), 8.65 (s, 1H), 8.20 (s, 1H), 6.80-7.08 (m, C*H*F2, 1H), 2.64 (s, 3H) ppm. ^{19}F NMR (300 MHz, *CDCl*$_3$): δ -117.21 and -130.70 ppm.

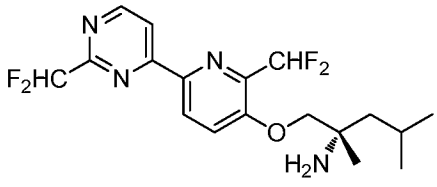


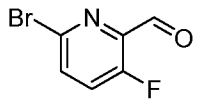
Part B. (S)-1-((4-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.016 g, 0.125 mmol) in tetrahydrofuran (2 mL) at 0 °C was added sodium hydride (8.03 mg, 0.334 mmol). To the resulting mixture, a solution of 4-(4-(difluoromethyl)-5-fluoropyridin-2 yl)-6-methylpyrimidine (0.02 g, 0.084 mmol) in THF was added slowly. The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched with ice-water, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to afford (*S*)-1-((4-(difluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4 dimethylpentan-2-amine (2 mg, 5.14 μmol, 6% yield) as a pale yellow solid. LCMS (ESI) *m/e* 351.2 [$(M+H)^+$, calcd for $C_{18}H_{25}F_2N_4O$ 351.2]; LC/MS retention time (method A1): t_R = 1.80 min; LC/MS retention time (method D): t_R = 1.40 min; LC/MS retention time (Method E): t_R = 1.08 min. ^{1}H NMR (400 MHz, *CD*$_3$*OD*): δ 9.09 (d, *J* = 1.2 Hz, 1H), 8.67 (d, *J* = 4.4 Hz, 2H), 8.30 (s, 1H), 7.10-7.40 (t, -C*H*F2, 1H), 4.28-4.37 (m, 2H), 2.64 (s, 3H), 1.63-1.87 (m, 3H), 1.45 (s, 3H), 0.98-1.07 (m, 6H) ppm. ^{19}F NMR (400 MHz, *CD*$_3$*OD*): δ -76.936 ppm.

Example 319

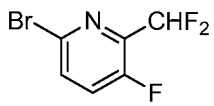
(*S*)-1-((2-(difluoromethyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





Part A: 6-bromo-3-fluoropicolinaldehyde

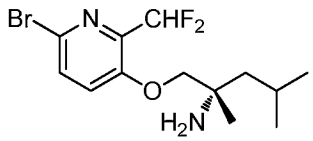
To a solution of (6-bromo-3-fluoropyridin-2-yl)methanol (4 g, 19.42 mmol) in DCM (80 mL) cooled to 0 °C was added Dess-Martin periodinane (12.35 g, 29.1 mmol). The mixture was warmed to room temperature and stirred for 14 h. The reaction mixture was quenched with saturated aqueous sodium bicarobonate (50 mL) and diluted with DCM (100 mL). The mixture was filtered through diatomaceous earth (Celite®). The bed was washed with DCM (100 mL) and the filtrate was transferred to a separating funnel. The aqueous layer was discarded and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford 6-bromo-3-fluoropicolinaldehyde (5.5 g, 27.0 mmol, 69.4 % yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.71 (dd, J = 8.8, 3.6 Hz, 1H), 7.50 – 7.46 (m, 1H).



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

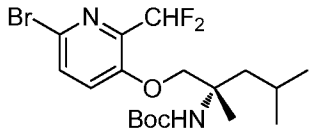
To a stirred solution of 6-bromo-3-fluoropicolinaldehyde (5 g, 24.51 mmol) in DCM (75 mL) cooled to -20 °C was added DAST (6.48 mL, 49.0 mmol) dropwise over 10 min. The reaction mixture was brought to room temperature gradually and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched carefully with saturated aqueous sodium bicarbonate solution (200 mL). The organic layer was separated out, dried over sodium sulfate, filtered, and concentrated under reduced pressure at 30 °C to afford 6-bromo-2-(difluoromethyl)-3-fluoropyridine (4.2 g, 18.58 mmol, 76 % yield) as a dark yellow solid which was carried forward without

further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.61 (m, 1H), 7.48 – 7.41 (m, 1H), 6.71 (t, J = 53.2 Hz, 1H).



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

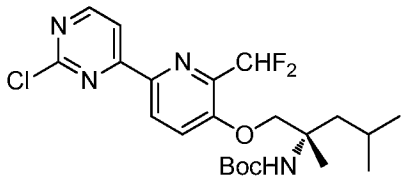
To a stirred solution of 6-bromo-2-(difluoromethyl)-3-fluoropyridine (3 g, 13.27 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (1.742 g, 13.27 mmol) in THF (20 mL) at 10 °C was added KOtBu 1M in THF (26.5 mL, 26.5 mmol) dropwise over 5 min. The cold bath was removed and the resulting solution was stirred at RT for 2 h. The reaction mixture was quenched with brine (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford (*S*)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (5 g, 9.64 mmol, 72.6 % yield) as a as brown semi-solid. LCMS (ESI) *m/e* 337.1 [$(M+H)^+$, calcd for $C_{13}H_{20}BrF_2N_2O$ 337.1]; LC/MS retention time (method B): t_R = 0.84 min.



Part D: (S)-tert-butyl (1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

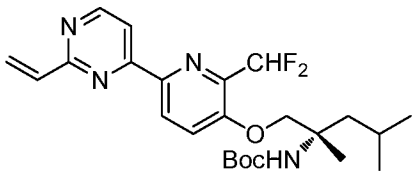
To a stirred solution of (*S*)-1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (4.5 g, 8.67 mmol) in a mixture of THF (40 mL) and water (40 mL) cooled to 10 °C was added K_2CO_3 (2.398 g, 17.35 mmol) and the mixture stirred for 5 min. BOC_2O (2.417 mL, 10.41 mmol) was added to and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was quenched with brine (200 mL) and extracted with ethyl acetate (200 mL). The organic layer was separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-20% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-((6-bromo-2-

(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (3.2 g, 7.32 mmol, 84 % yield) as a yellow oil. LCMS (ESI) *m/e* 437.1 $[(M+H)^+$, calcd for $C_{18}H_{28}BrF_2N_2O_3$ 437.1]; LC/MS retention time (method B): t_R = 1.29 min.



Part E: (S)-tert-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

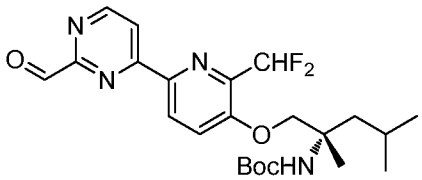
A solution of 2,4-dichloropyrimidine (200 mg, 1.342 mmol) and (*S*)-*tert*-butyl (1-((6-bromo-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (587 mg, 1.342 mmol) in 1,4-dioxane (8 mL) was purged with nitrogen for 5 min. $Pd(Ph_3P)_4$ (78 mg, 0.067 mmol) was added followed by bis(tributyltin) (0.677 mL, 1.342 mmol). The reaction mixture was heated in a microwave at 150 °C for 1h. The reaction mixture was diluted with ethyl acetate (10 mL), filtered thorough diatomaceous earth (Celite®) and concentrated under reduced pressure to afford a black residue. The residue was purified by silica gel chromatography (15% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (500 mg, 1.062 mmol, 20% yield) as colorless semi-solid. LCMS (ESI) *m/e* 471.2 $[(M+H)^+$, calcd for $C_{22}H_{30}ClF_2N_4O_3$ 471.2]; LC/MS retention time (method B): t_R = 1.20 min.



Part F: (S)-tert-butyl (1-((2-(difluoromethyl)-6-(2-vinylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of (*S*)-*tert*-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-(difluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (500 mg, 1.062 mmol) and 2,4,6-trivinylcyclotriboroxane pyridine complex (256 mg, 1.062 mmol) in 1,4-dioxane (12 mL) was added cesium carbonate (865 mg, 2.65 mmol) in

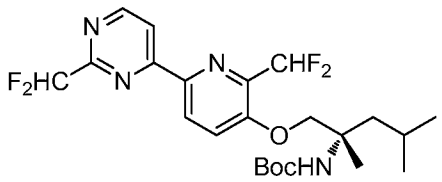
water (1.2 mL). The reaction mixture was purged with nitrogen for 5 min and $PdCl_2(dppf)$-CH_2Cl_2 adduct (87 mg, 0.106 mmol) was added. The reaction mixture was heated to 90 °C for 6 h. The reaction mixture was diluted with ethyl acetate (25 mL), filtered through diatomaceous earth (Celite®) and the filtrate was evaporated under reduced pressure to afford a brown residue. The residue was purified by silica gel chromatography (20% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-vinylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (330 mg, 0.713 mmol, 67% yield) as yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 5.20 Hz, 1H), 8.63 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 5.20 Hz, 1H), 7.50 (m, 1H), 7.00-6.69 (m, 3H), 5.75 (m, 1H), 4.38-4,36 (m, 1H), 4.16-4.14 (m, 1H), 1.88-1.75 (m, 2H), 1.51-1.54 (m, 1H), 1.40 (s, 3H), 1.0- 0.98 (m, 6H) ppm.



Part G: (S)-tert-butyl (1-((2-(difluoromethyl)-6-(2-formylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

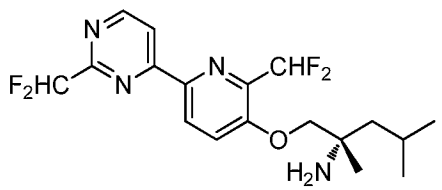
A solution of (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-vinylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (330 mg, 0.713 mmol) and 2,6-lutidine (0.166 mL, 1.427 mmol) in a mixture of 1,4-dioxane (7 mL) : water (3 mL) was cooled to 0 °C. Osmium tetroxide, 2.5% in *t*-butanol (0.269 mL, 0.021 mmol) was added. The reaction mixture was stirred at 0 °C for 5 min and sodium periodate (610 mg, 2.85 mmol) was added. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with ethyl acetate (50 mL) and filtered through diatomaceous earth (Celite®). The filtrate was washed with water (25 mL) and brine (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford a brown oil. The residue was purified by silica gel chromatography (0-40% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-formylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-

dimethylpentan-2-yl)carbamate (200 mg, 0.431 mmol, 60% yield) as a yellow semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 9.04 (d, J = 5.20 Hz, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.52 (d, J = 5.20 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 6.88 (t, J = 54.4 Hz, 3H), 5.75 (m, 1H), 4.41-4.39 (m, 1H), 4.19-4.17 (m, 1H), 1.92-1.77 (m, 2H), 1.51-1.54 (m, 1H), 1.40 (s, 3H), 1.0- 0.98 (m, 6H) ppm.



Part H: (S)-tert-butyl (1-((2-(difluoromethyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-formylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (200 mg, 0.431 mmol) in DCM (5 mL) cooled to -78 °C was added DAST (0.114 mL, 0.861 mmol) dropwise over 5 min. The reaction mixture was gradually brought to 0 °C and stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous bicarbonate solution (20 mL) and extracted with DCM (25 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a dark red residue. The residue was purified by silica gel chromatography (0-20% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (100 mg, 0.206 mmol, 48% yield) as a yellow semi-solid. LCMS (ESI) *m/e* 487.2 [$(M+H)^+$, calcd for $C_{23}H_{31}F_4N_4O_3$ 487.2]; LC/MS retention time (Method G): t_R = 3.73 min.



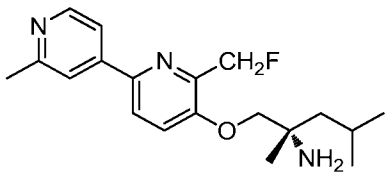
Part I: (S)-1-((2-(difluoromethyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

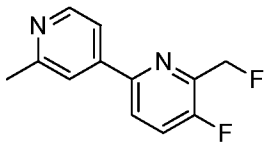
A solution of (*S*)-*tert*-butyl (1-((2-(difluoromethyl)-6-(2-

(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (120 mg, 0.247 mmol) in DCM (1 mL) was cooled to 0 °C was added HCl 4M in 1,4-dioxane (0.617 mL, 2.467 mmol) and the cold bath was removed. The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the solid residue was washed with ether (10 mL). The residue was basified with saturated aqueous sodium bicarbonate solution (25 mL) and extracted with ethyl acetate (2x20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford a yellow sticky solid. The sticky solid obtained was dissolved in acetonitrile:water (1:3) and lyophilized overnight to afford (*S*)-1-((2-(difluoromethyl)-6-(2-(difluoromethyl)pyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (35 mg, 0.087 mmol, 35% yield) as a yellow sticky solid. LCMS (ESI) *m/e* 387.2 [$(M+H)^+$, calcd for $C_{18}H_{23}F_4N_4O$ 387.2]; LC/MS retention time (method H): t_R = 1.27 min; LC/MS retention time (method NA): t_R = 2.03 min. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.93 (d, *J* = 5.20 Hz, 1H), 8.65 (d, *J* = 11.20 Hz, 1H), 8.44 (d, *J* = 5.20 Hz, 1H), 8.44 (d, *J* = 8.80 Hz, 1H), 6.58-7.01 (m, 2H), 3.89 (s, 2H), 1.79-1.82 (m, 1H), 1.51-1.54 (m, 2H), 1.28 (s, 3H), 0.98-1.01 (m, 6H) ppm.

Example 320

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

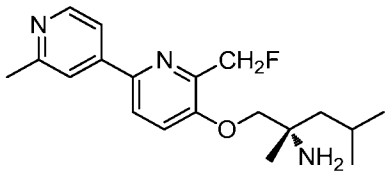




Part A. 5-fluoro-6-(fluoromethyl)-2'-methyl-2,4'-bipyridine

A mixture of (2-methylpyridin-4-yl)boronic acid (0.05 g, 0.365 mmol), 6-bromo-3-fluoro-2-(fluoromethyl)pyridine (prepared as described in Example 279)

(0.076 g, 0.365 mmol), Cs_2CO_3 (0.238 g, 0.730 mmol) in 1,4-dioxane (3 mL) and water (0.3 mL) was purged with nitrogen gas for 10 min. $PdCl_2(dppf)$ (0.013 g, 0.018 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas for another 10 min. The reaction mixture was heated at 90°C overnight. The reaction mixture was concentrated, dissolved in ethyl acetate (20 mL) and washed with brine. The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford the crude 5-fluoro-6-(fluoromethyl)-2'-methyl-2,4'-bipyridine (62 mg, 0.160 mmol, 44% yield) as a brown solid. LCMS (ESI) *m/e* 221.2 [$(M+H)^+$, calcd for $C_{12}H_{11}F_2N_2$, 221.21]; LC/MS retention time (method A1): t_R = 1.80 min.

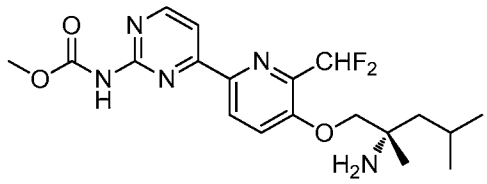


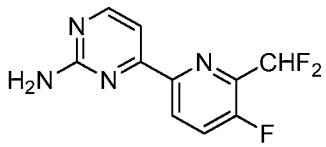
Part B. (S)-1-((6-(fluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.045 g, 0.341 mmol) in tetrahydrofuran (2 mL) at 0 °C was added sodium hydride (0.022 g, 0.908 mmol). To the reaction mixture a solution of 5-fluoro-6-(fluoromethyl)-2'-methyl-2,4'-bipyridine (0.05 g, 0.227 mmol) in THF was added slowly and the mixture allowed to stir overnight at room temperature. The reaction mixture was quenched with ice water, diluted with brine and ethyl acetate. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford (*S*)-1-((6-(fluoromethyl)-2'-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (17 mg, 0.048 mmol, 21% yield) as a pale yellow solid. LCMS (ESI) *m/e* 332.3 [$(M+H)^+$, calcd for $C_{19}H_{27}FN_3O$, 332. 2]; LC/MS retention time (method H): t_R = 1.43 min. ^1H NMR (400 MHz, Methanol-*d4*): δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.08-8.10 (m, 1H), 7.97 (s, 1H), 7.86-7.91 (m, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 5.56-5.78 (m, 2H), 4.15-4.25 (m, 2H), 2.63 (s, 3H), 1.80-1.93 (m, 2H), 1.65-1.72 (m, 1H), 1.49 (s, 3H), 0.98-1.07 (m, 6H) ppm.

Example 323

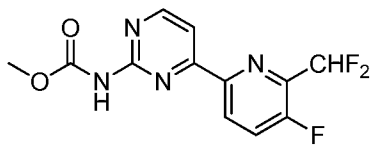
(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate





Part A. 4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-amine

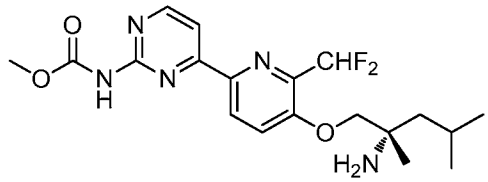
A solution methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.1 g, 0.533 mmol), 6-bromo-2-(difluoromethyl)-3-fluoropyridine (prepared as described in Example 322) (0.120 g, 0.533 mmol) and hexamethylditin (0.111 mL, 0.533 mmol) in 1,4-dioxane (5 mL) was flushed with nitrogen for 10 min. $Pd(Ph_3P)_4$ (0.031 g, 0.027 mmol) was added and the reaction mixture was flushed with nitrogen for 5 min. The reaction mixture was heated in a microwave at 150 °C for 90 min. The reaction mixture was then filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by silica-gel chromatography (pet ether/ethyl acetate (50-100%)) to afford 4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-amine (0.08 g, 0.280 mmol, 52% yield). LCMS (ESI) *m/e* 241.2 [$(M+H)^+$, calcd for $C_{10}H_8F_3N_4$ 241.1]; LC/MS retention time (Method G): t_R = 1.66 min.



Part B. methyl (4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-yl)carbamate

To a solution of 4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-

amine (0.08 g, 0.280 mmol) in $CHCl_3$ (2 mL) was added pyridine (0.226 mL, 2.80 mmol) followed by DMAP (3.42 mg, 0.028 mmol), and methyl chloroformate (0.043 mL, 0.560 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (80 mL). The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-yl)carbamate (0.09 g, 0.100 mmol, 36% yield). LCMS (ESI) *m/e* 299.0 $[(M+H)^+$, calcd for $C_{12}H_{10}F_3N_4O_2$ 299.1]; LC/MS retention time (Method G): t_R = 2.28 min.

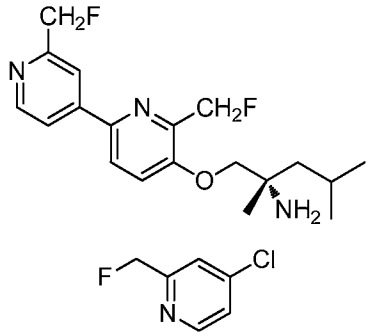


Part C. (S)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate

To a solution of methyl (4-(6-(difluoromethyl)-5-fluoropyridin-2-yl)pyrimidin-2-yl)carbamate (0.03 g, 0.049 mmol) in DMF (3 mL) cooled to 0 °C was added NaH (3.94 mg, 0.099 mmol) followed by (*S*)-2-amino-2,4-dimethylpentan-1-ol (6.47 mg, 0.049 mmol). The mixture was then stirred at room overnight. The reaction mixture was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (20 mL) . The filtrate was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate (0.006 g, 0.014 mmol, 28% yield) as a pale yellow solid. LCMS (ESI) *m/e* 410.3 $[(M+H)^+$, calcd for $C_{19}H_{26}F_2N_5O_3$ 410.2]; LC/MS retention time (method H): t_R = 1.25 min; LC/MS retention time (method I): t_R = 1.01 min. ^{1}H NMR(400 MHz, methanol-d_4): δ 8.66-8.69 (m, 2H), 8.04-8.06 (m, 1H), 7.75 (d, *J* = 8.80 Hz, 1H), 7.03 (t, *J* = 107.60 Hz, 1H), 4.02-4.09 (m, 2H), 3.84 (s, 3H), 1.86-1.92 (m, 1H), 1.55-1.68 (m, 2H), 1.32 (s, 3H), 1.00-1.04 (m, 6H) ppm.

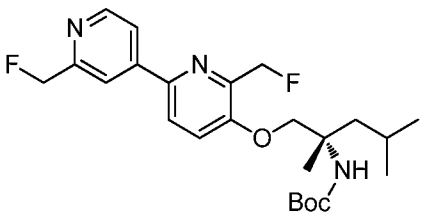
Example 324

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



Part A. 4-chloro-2-(fluoromethyl)pyridine

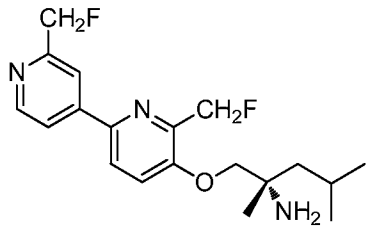
To a solution of (4-chloropyridin-2-yl)methanol (1 g, 6.97 mmol) in DCM (40 mL) at -78 °C was slowly added diethylaminosulfur trifluoride (2.245 g, 13.93 mmol). The reaction mixture was stirred at -78 °C for 10 min. The reaction mixture was quenched with aqueous 10% $NaHCO_3$ solution and diluted with dichloromethane (50 mL). The organic layer was separated, diluted with dichloromethane, filtered through the celite, dried over Na_2SO_4, filtered, and concentrated under pressure to afford 4-chloro-2-(fluoromethyl)pyridine (0.5 g) as a violet oil. LCMS (ESI) *m/e* 146.4 [$(M+H)^+$, calcd for C_6H_6ClFN, 146.0]; LC/MS retention time (method B): t_R = 0.68 min.



Part B. (S)-tert-butyl (1-((2',6-bis(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-2-(fluoromethyl)pyridine (50 mg, 0.343 mmol), (*S*)-*tert*-butyl (1-((6-bromo-2-(fluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (144 mg, 0.343 mmol), and 1,1,1,2,2,2-hexamethyldistannane (113 mg, 0.343 mmol) in DMF (3 mL) was purged with nitrogen gas for 10 min. $Pd(Ph_3P)_4$ (19.85 mg, 0.017 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas for another 10 min. The reaction mixture was irradiated in a microwave at 120 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate

(20 mL) and washed with brine. The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-((2',6-bis(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (58 mg, 0.129 mmol, 38% yield) as a brown oil. LCMS (ESI) *m/e* 450.2 [$(M+H)^+$, calcd for $C_{24}H_{34}F_2N_3O_3$, 450.3]; LC/MS retention time (Method G): t_R = 3.80 min.

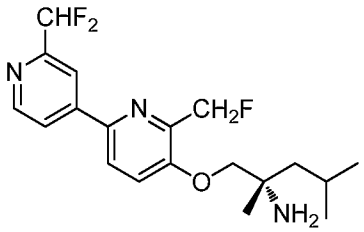


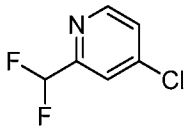
Part C. (S)-1-((2',6-bis(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-((2',6-bis(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (90 mg, 0.200 mmol) in dichloromethane (3 mL) was added hydrogen chloride (0.501 mL, 2.002 mmol). The reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was concentrated, quenched with 10% aqueous $NaHCO_3$ solution and diluted with dichloromethane (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford (*S*)-1-((2',6-bis(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (2 mg, 5.49 µmol, 3% yield) as a yellow solid. LCMS (ESI) *m/e* 350.3 [$(M+H)^+$, calcd for $C_{19}H_{26}F_2N_3O$, 350.2]; LC/MS retention time (method H): t_R = 1.39 min; LC/MS retention time (method I): t_R = 0.83 min. ^{1}H NMR(400 MHz, Methanol-*d4*): δ 8.67 (d, *J* = 5.2 Hz, 1H), 8.21-8.24 (m, 1H), 8.15 (s, 1H), 8.01 (d, *J* = 5.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 5.49-5.67 (m, 4H), 3.88 (s, 2H), 1.75-1.87 (m, 1H), 1.39-1.46 (m, 2H), 1.16 (s, 3H), 0.89-0.98 (m, 6H) ppm.

Example 325

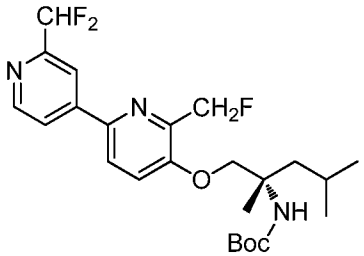
(*S*)-1-((2'-(difluoromethyl)-6-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine





Part A. 4-chloro-2-(difluoromethyl)pyridine

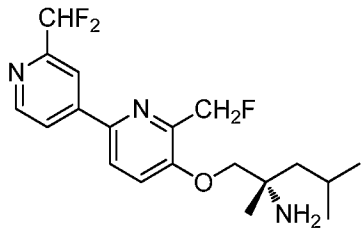
To a solution of 4-chloropicolinaldehyde (2 g, 14.13 mmol) in DCM (30 mL) at -78 °C was slowly added diethylaminosulfur trifluoride (4.55 g, 28.3 mmol). The reaction mixture was stirred at -78 °C for 1 h. The reaction mixture was quenched with aqueous 10% $NaHCO_3$ solution and diluted with dichloromethane (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under pressure to afford 4-chloro-2-(difluoromethyl)pyridine (1.8 g, 11.01 mmol, 78% yield) as a brown oil. LCMS (ESI) *m/e* 164.0 [$(M+H)^+$, calcd for $C_6H_5ClF_2N$, 164.0]; LC/MS retention time (method B): t_R = 0.81 min.



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

A mixture of 4-chloro-2-(difluoromethyl)pyridine (50 mg, 0.306 mmol), (*S*)-*tert*-butyl (1-((6-bromo-2-(fluoromethyl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (128 mg, 0.306 mmol), and 1,1,1,2,2,2-hexamethyldistannane (100 mg, 0.306 mmol) in DMF (4 mL) was purged with nitrogen gas for 10 min. $Pd(Ph_3P)_4$ (17.66 mg, 0.015 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas for another 10 min. The reaction mixture was irradiated in a microwave at 120 °C for 1 h. The reaction mixture was concentrated, dissolved in

ethyl acetate (20 mL) and washed with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (pet ether/ethyl acetate (20-40%)) to afford (*S*)-*tert*-butyl (1-((2'-(difluoromethyl)-6-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (86 mg, 0.184 mmol, 60% yield) as a pale yellow solid. LCMS (ESI) *m/e* 468.3 $[(M+H)^+$, calcd for $C_{24}H_{33}F_3N_3O_3$, 468. 2]; LC/MS retention time (method B): t_R = 1.18 min.

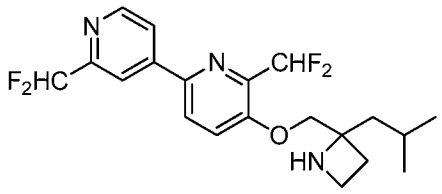


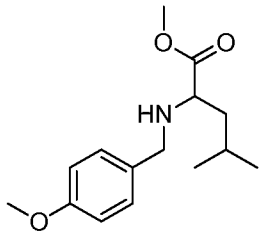
Part C. (S)-1-((2'-(difluoromethyl)-6-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-((2'-(difluoromethyl)-6-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (130 mg, 0.278 mmol) in dichloromethane (3 mL), was added hydrogen chloride (0.695 mL, 2.78 mmol). The reaction mixture was allowed to stir for 1 h at room temperature. The reaction mixture was concentrated, quenched with 10% aqueous $NaHCO_3$ solution and diluted with dichloromethane (20 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford (*S*)-1-((2'-(difluoromethyl)-6-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (6.3 mg, 0.016 mmol, 6% yield) as a pale yellow solid. LCMS (ESI) *m/e* 368.3 $[(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$ 368.40]; LC/MS retention time (method H): t_R = 1.49 min; LC/MS retention time (method I): t_R = 1.19 min. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.76 (d, *J* = 5.2 Hz, 1H), 8.20-8.33 (m, 2H), 8.19 (d, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 6.89-7.17 (t, -C*H*F2, 1H), 5.55-5.68 (m, 2H), 3.90 (s, 2H), 1.73-1.87 (m, 1H), 1.37-1.48 (m, 2H), 1.16 (s, 3H), 0.89-0.97 (m, 6H) ppm.

Example 326

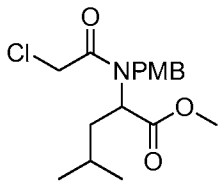
2',6-bis(difluoromethyl)-5-((2-isobutylazetidin-2-yl)methoxy)-2,4'-bipyridine





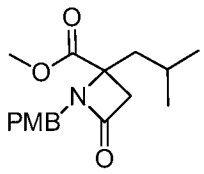
Part A. methyl 2-((4-methoxybenzyl)amino)-4-methylpentanoate

A solution of 4-methoxybenzaldehyde (4.18 mL, 37.2 mmol) in methanol (40 mL) was cooled to 0 °C and TEA (4.32 mL, 31.0 mmol) was added followed by 4-methoxybenzaldehyde (4.18 mL, 37.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 90 min. The reaction mixture was cooled to 0 °C and $NaBH_4$ (2.35 g, 62.0 mmol) was added in portions. The reaction mixture was warmed to room temperature and stirred for 90 min. The reaction mixture was again cooled to 0 °C and additional $NaBH_4$ (2.61 g, 68.9 mmol) was added in portions. The reaction mixture was warmed to room temperature and stirred for 20 min. The reaction mixture was cooled to 0°C and quenched with saturated aqueous ammonium chloride (25 mL). The mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL) and brine (1 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (0-20% pet ether:ethyl acetate) to afford methyl 2-((4-methoxybenzyl)amino)-4-methylpentanoate (4.4 g, 13.76 mmol, 44% yield) as a brown semi-solid. LCMS (ESI) *m/e* 266.1 $[(M+H)^+$, calcd for $C_{15}H_{24}NO_3$ 266.2]; LC/MS retention time (method B): t_R = 0.79 min.



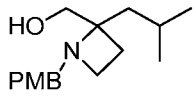
Part B. methyl 2-(2-chloro-N-(4-methoxybenzyl)acetamido)-4-methylpentanoate

A solution of methyl 2-((4-methoxybenzyl)amino)-4-methylpentanoate (8 g, 30.1 mmol) in THF (50 mL) was cooled to 0 °C and propylene oxide (21.35 mL, 301 mmol) was added followed by dropwise addition of 2-chloroacetyl chloride (3.60 mL, 45.2 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with water (50 mL) and extracted in to ethyl acetate (2 x 100 mL). The ethyl acetate layer was washed with water (1 x 20 mL) and brine (1 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford methyl 2-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-4-methylpentanoate (10 g, 27.2 mmol, 90% yield) as a pale yellow liquid. LCMS (ESI) *m/e* 342.1 [$(M+H)^+$, calcd for $C_{17}H_{25}ClNO_4$ 342.1]; LC/MS retention time (Method C): t_R = 1.09 min.



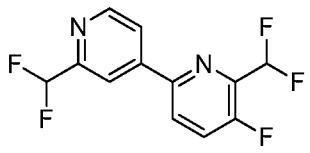
Part C. methyl 2-isobutyl-1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxylate

To a solution of methyl 2-(2-chloro-*N*-(4-methoxybenzyl)acetamido)-4-methylpentanoate (3.0 g, 8.78 mmol) in acetonitrile (30 mL), Cs_2CO_3 (5.72 g, 17.55 mmol) was added at room temperature. The reaction mixture was heated to 75 °C overnight. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL) brine (1 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via silica gel chromatography (20-50% pet ether:ethyl acetate) to afford methyl 2-isobutyl-1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxylate (550 mg, 1.801 mmol, 21% yield) as a colorless liquid. LCMS (ESI) *m/e* 306.1 [$(M+H)^+$, calcd for $C_{17}H_{24}NO_4$ 306.2]; LC/MS retention time (Method C): t_R = 1.03 min.



Part D. (2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methanol

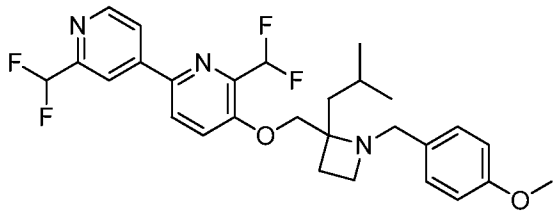
To a solution of methyl 2-isobutyl-1-(4-methoxybenzyl)-4-oxoazetidine-2-carboxylate (500 mg, 1.637 mmol) in THF (10 mL) cooled to -30 °C was added 2.4M LAH in THF (1.364 mL, 3.27 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was cooled to 0°C, quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL) and brine (1 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methanol (350 mg, 1.329 mmol, 81% yield) as a brown semi-solid. LCMS (ESI) *m/e* 264.2 [$(M+H)^+$, calcd for $C_{16}H_{26}NO_2$ 264.2]; LC/MS retention time (Method G): t_R = 1.59 min.



Part E. 2',6-bis(difluoromethyl)-5-((2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methoxy)-2,4'-bipyridine

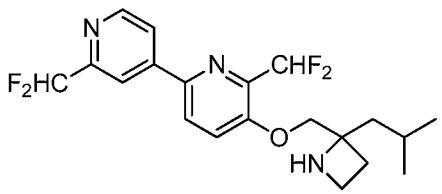
To a solution of (2-(difluoromethyl)pyridin-4-yl)boronic acid (prepared as in Example 123 (509 mg, 2.94 mmol) in EtOH (20 mL) and THF (10 mL) in a sealed tube was added tripotassium phosphate 2 M in water (2.323 mL, 4.65 mmol). The mixture was purged with argon for 5 min. XPhos 2nd generation precatalyst (36.6 mg, 0.046 mmol) and 6-bromo-2-(difluoromethyl)-3-fluoropyridine (prepared as described in Example 322) (350 mg, 1.549 mmol) were added. The vessel was sealed and heated to 80 °C for 12h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (25 mL). The solution was filtered through diatomaceous earth (Celite®) and the filtrate was evaporated under reduced pressure to afford dark brown residue. The residue was purified via silica gel chromatography (0-30% pet ether:ethyl acetate) to afford 2',6-bis(difluoromethyl)-5-fluoro-2,4'-bipyridine (250 mg, 0.912 mmol, 59% yield) as dark yellow solid. LCMS

(ESI) *m/e* 275.0 [(M+H)$^+$, calcd for $C_{12}H_5F_5N_2$ 275.1]; LC/MS retention time (Method G): t_R = 2.54 min.



Part F. 2',6-bis(difluoromethyl)-5-((2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methoxy)-2,4'-bipyridine

To a solution of (2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methanol (192 mg, 0.729 mmol) in THF (5 mL) at 0°C was added KO*t*-Bu, 1M in THF (0.729 mL, 0.729 mmol). The mixture was then stirred at 0 °C for 5 min. 2',6-Bis(difluoromethyl)-5-fluoro-2,4'-bipyridine (200 mg, 0.729 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with brine (25 mL) and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20-60% EtOAc in hexanes). The product obtained was further purified by Preparative HPLC (10 mM ammonium acetate in water and acetonitrile) to afford 2',6-bis(difluoromethyl)-5-((2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methoxy)-2,4'-bipyridine (150 mg, 0.145 mmol, 20% yield) as a yellow oil. LCMS (ESI) *m/e* 518.2 [(M+H)$^+$, calcd for $C_{28}H_{32}F_4N_3O_2$, 518.2]; LC/MS retention time (Method G): t_R = 3.57 min.



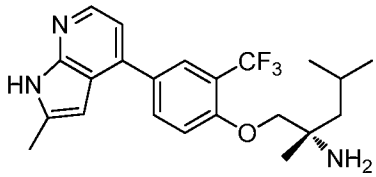
Part G. 2',6-bis(difluoromethyl)-5-((2-isobutylazetidin-2-yl)methoxy)-2,4'-bipyridine

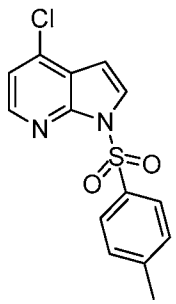
To a solution of 2',6-bis(difluoromethyl)-5-((2-isobutyl-1-(4-methoxybenzyl)azetidin-2-yl)methoxy)-2,4'-bipyridine (100 mg, 0.097 mmol) in dichloromethane (5 mL)/water (2 mL) was added DDQ (32.9 mg, 0.145 mmol). The mixture was then stirred at room temperature for 1h. The reaction mixture was

diluted with dichloromethane (50 mL) and quenched with 10% Na_2CO_3 solution (50 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-10% MeOH in DCM) to afford 2',6-bis(difluoromethyl)-5-((2-isobutylazetidin-2-yl)methoxy)-2,4'-bipyridine (17 mg, 0.042 mmol, 44% yield) as a yellow sticky solid. LCMS (ESI) *m/e* 398.2 [$(M+H)^+$, calcd for $C_{20}H_{24}F_4N_3O$ 398.2]; LC/MS retention time (Method G): t_R = 1.61 min. ^1H NMR(400 MHz, Methanol-d_4): δ 8.72 (d, *J* = 5.20 Hz, 1H), 8.37 (s, 1H), 8.28 (d, *J* = 8.80 Hz, 1H), 8.20-8.22 (m, 1H), 7.82 (d, *J* = 8.80 Hz, 1H), 6.67-7.12 (m, 2H), 4.30-4.43 (m, 2H), 3.63-3.78 (m, 1H), 3.57-3.61 (m, 1H), 2.43-2.48 (m, 2H), 1.93-1.98 (m, 1H), 1.84-1.89 (m, 1H), 1.72-1.75 (m, 1H), 0.95-0.99 (m, 6H) ppm.

Example 327

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

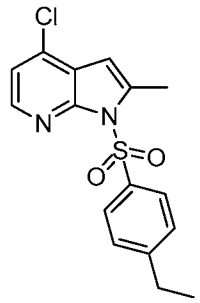




Part A: 4-chloro-1-tosyl-1H-pyrrolo[2,3-b]pyridine

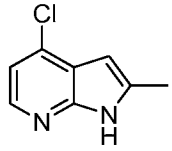
To a stirred solution of 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine (0.82 g, 5.37 mmol) in THF (16 mL) and DMF (8.00 mL) was added sodium *tert*-butoxide (1.291 g, 13.44 mmol) and *p*-toluenesulfonyl chloride (2.049 g, 10.75 mmol). The mixture was stirred at room temperature for 2.5 h. The reaction mixture was quenched with saturated ammonium chloride solution (60 mL) and extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel

chromatography (ethyl acetate and pet ether) to afford 4-chloro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.6 g, 4.85 mmol, 90% yield) as a white semi-solid. LCMS (ESI) *m/e* 307.0 [$(M+H)^+$, calcd for $C_{14}H_{12}ClN_2O_2S$, 307.0]; LC/MS retention time (method A2); t_R = 2.11 min.



Part B: 4-chloro-1-((4-ethylphenyl)sulfonyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine

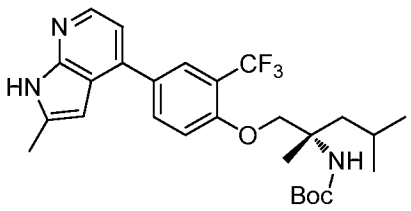
A solution of 4-chloro-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1.5 g, 4.89 mmol) in THF (20 mL) was cooled to -78 °C. LDA (6.11 mL, 12.22 mmol) was added at -78 °C and stirred at this temperature for 1 h. Methyl iodide (0.611 mL, 9.78 mmol) was then added and stirred at -78 °C for 1 h. The reaction mixture was then allowed to warm to room temperature and stirred for 50 min. The reaction mixture cooled to 0 °C, quenched by addition of saturated ammonium chloride solution (10 mL), and extracted with ethyl acetate (3 x 20 mL). The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC to afford 4-chloro-1-((4-ethylphenyl)sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.68 g, 1.990 mmol, 36% yield) as a yellow semi-solid. LCMS (ESI) *m/e* 335.0 [$(M+H)^+$, calcd for $C_{16}H_{16}ClN_2O_2S$, 335.1]; LC/MS retention time (Method A1); t_R = 2.60 min.



Part C: 4-chloro-2-methyl-1H-pyrrolo[2,3-b]pyridine

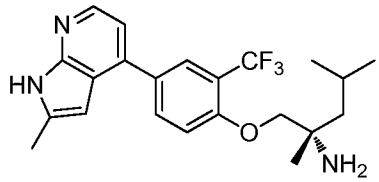
To a solution of 4-chloro-1-((4-ethylphenyl)sulfonyl)-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.2 g, 0.585 mmol) in MeOH (4 mL) was added 5M NaOH

solution (0.585 mL, 2.93 mmol) at room temperature. The whole mixture was heated at 70 °C for 5 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with ethyl acetate (15 mL) and water (10 mL). The organic layer was re-extracted with ethyl acetate (2 x 10 mL). The combined organics were dried and concentrated to afford 4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.1 g, 0.504 mmol, 86% yield) as a pale yellow solid. LCMS (ESI) *m/e* 167.2 [$(M+H)^+$, calcd for $C_8H_8ClN_2$, 167.03]; LC/MS retention time (Method A1); t_R = 1.82 min.



Part D: (S)-tert-butyl (2,4-dimethyl-1-(4-(2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate

A mixture of 4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (0.028 g, 0.141 mmol), (*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 215, Parts A and B) (0.071 g, 0.141 mmol), and Cs_2CO_3 (0.069 g, 0.212 mmol) in THF (2 mL) and water (0.667 mL) was purged with nitrogen for 15 min. XPhos 2nd generation precatalyst (0.017 g, 0.021 mmol) was added and nitrogen gas was bubbled through reaction mixture for 5 min and stirred at 65 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with THF (10 mL) and filtered through diatomaceous earth (Celite®). The bed was washed with excess THF. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate and pet ether) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.032 g, 0.062 mmol, 44% yield) as a pale yellow oil. LCMS (ESI) *m/e* 506.2 [$(M+H)^+$, calcd for $C_{27}H_{36}F_3N_3O_3$, 506.26]; LC/MS retention time (Method A1); t_R = 2.80 min.

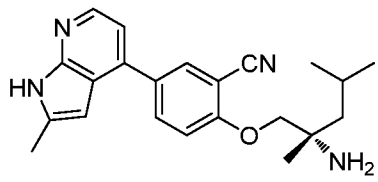


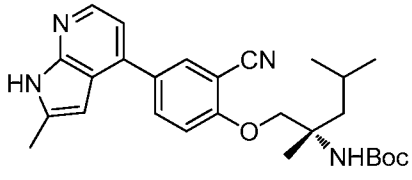
Part E: (S)-2,4-dimethyl-1-(4-(2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine

A solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-yl)carbamate (0.032 g, 0.062 mmol) in MeOH (1.5 mL) cooled to 0 °C under a nitrogen atmosphere was stirred for 10 min. TFA (1.5 mL, 19.47 mmol) was added dropwise over a period of 1 min and the mixture warmed to room temperature and stirred for 4 h. The mixture was concentrated under reduced pressure at 28 °C. The compound was purified by reverse phase HPLC purification (Method D) to afford (*S*)-2,4-dimethyl-1-(4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine, 2 TFA (0.015 g, 0.022 mmol, 35% yield) as a pale yellow solid. LCMS (ESI) *m/e* 404.3 [(M-H)$^+$, calcd for $C_{22}H_{25}F_3N_3O$, 404.20]; LC/MS retention time (method H); t_R = 1.86 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.25 (d, *J* = 5.6 Hz, 1H), 8.12 - 8.08 (m, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 6.52 (s, 1H), 4.36 (d, *J* = 10.4 Hz, 1H), 4.28 (d, *J* = 10.4 Hz, 1H), 2.57 (s, 3H), 1.95 - 1.85 (m, 2H), 1.79 - 1.72 (m, 1H), 1.57 (s, 3H), 1.07 (m, 6H) ppm.

Example 328

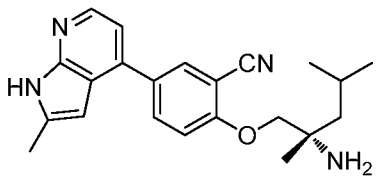
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzonitrile





Part A: (S)-tert-butyl (1-(2-cyano-4-(2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-2-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (prepared as described in Example 327) (0.029 g, 0.146 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 (0.074 g, 0.161 mmol) (prepared as in Example 86, Parts A and B), and Cs_2CO_3 (0.071 g, 0.219 mmol) in THF (2 mL) and water (0.667 mL). The mixture was purged with nitrogen for15 min. XPhos 2nd generation precatalyst (0.017 g, 0.022 mmol) was added, then purged with nitrogen gas for 5 min. The mixture was then stirred at 65 °C for 5 h. The reaction mixture was cooled to room temperature and diluted with THF (10 mL) and filtered through diatomaceous earth (Celite®). The bed was washed with excess THF. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (ethyl acetate and pet ether) to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.065 g, 0.133 mmol, 91 % yield) as a pale yellow oil. LCMS (ESI) *m/e* 463.2 [$(M+H)^+$, calcd for $C_{27}H_{35}N_4O_3$, 463.26]; LC/MS retention time (method H); t_R = 2.65 min.



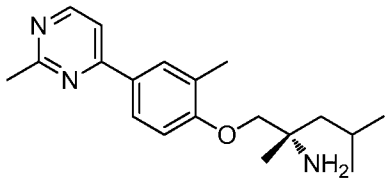
Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methyl-1H-pyrrolo[2,3-b]pyridin-4-yl)benzonitrile

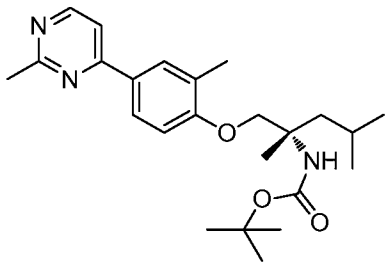
A solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.065 g, 0.133 mmol) in MeOH (1.5 mL) cooled to 0 °C under a nitrogen atmosphere was stirred for 10 min. TFA (1.5 mL, 19.47 mmol) was added dropwise over a period of 1 min and the mixture warmed to room temperature and allowed to stir for 4 h. The mixture was concentrated under reduced pressure at 28 °C. The residue was washed with diethyl ether (2 x 10 mL), then dried under vacuum for 10 min. The product was lyophilized to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzonitrile, TFA (0.025 g, 0.064 mmol, 48% yield) as a pale yellow

solid. LCMS (ESI) *m/e* 363.2 [(M+H)$^+$, calcd for $C_{22}H_{27}N_4O$, 363.21]; LC/MS retention time (method H); t_R = 2.01 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.13 (d, *J* = 5.0 Hz, 1H), 8.07 - 8.04 (m, 2H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 5.0 Hz, 1H), 6.38 (s, 1H), 4.08-4.03 (m, 2H), 2.49 (s, 3H), 1.90 - 1.86 (m, 1H), 1.66 - 1.56 (m, 2H), 1.35 - 1.23 (s, 3H), 1.05-1.02 (m, 6H) ppm.

Example 329

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

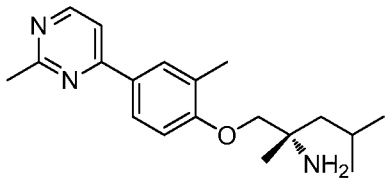




Part A: (S)-tert-butyl (2,4-dimethyl-1-(2-methyl-4-(2-methylpyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate

A mixture of (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)phenoxy) pentan-2-yl)carbamate (prepared using the procedure described in Example 285) (0.070 g, 0.156 mmol), 4-chloro-2-methylpyrimidine (0.02 g, 0.156 mmol), and tripotassium phosphate (2M Solution) (0.5 mL, 1.00 mmol) in THF (2 mL) was purged with nitrogen for15 min. XPhos 2nd generation precatalyst (0.037 g, 0.047 mmol) was added and the mixture purged for a further 5 min. The reaction mixture was then stirred at 75 °C for 2.5 h. The reaction mixture was cooled to room temperature and diluted with THF (15 mL) and filtered through diatomaceous earth (Celite®). The bed was washed with excess of THF. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (ethyl acetate and pet ether) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(2-methylpyrimidin-4-yl)phenoxy)pentan-2-

yl)carbamate (0.018 g, 0.036 mmol, 23% yield) as a yellow oil. LCMS (ESI) *m/e* 414.4 [(M+H)$^+$, calcd for $C_{24}H_{36}N_3O_3$, 414.26]; LC/MS retention time (method A2); t_R = 2.30 min.

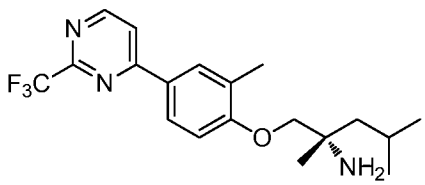


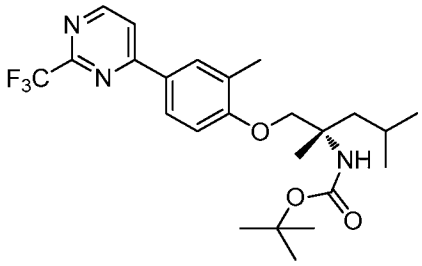
Part B: (S)-2,4-dimethyl-1-(2-methyl-4-(2-methylpyrimidin-4-yl)phenoxy)pentan-2-amine

A solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(2-methylpyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate (0.018 g, 0.036 mmol) in MeOH (1.5 mL) cooled to 0 °C under a nitrogen atmosphere was stirred for 10 min. TFA (1.5 mL, 19.47 mmol) was added dropwise over a period of 1 min and the mixture warmed to room temperature and allowed to stir for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (method B) to afford (*S*)-2,4-dimethyl-1-(2-methyl-4-(2-methylpyrimidin-4-yl)phenoxy)pentan-2-amine, TFA (5.5 mg, 0.036 mmol, 43% yield). LCMS (ESI) *m/e* 314.2 [(M+H)$^+$, calcd for $C_{19}H_{28}N_3O$,314.21]; LC/MS retention time (Method E); t_R = 1.02 min. LC/MS retention time (method D); t_R = 1.29 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.64 (d, *J* = 5.60 Hz, 1H), 8.07-8.09 (m, 2H), 7.81 (d, *J* = 5.60 Hz, 1H), 7.12-7.15(m, 1H), 4.12-4.22 (m, 2H), 2.75 (s, 3H), 2.41 (s, 3H), 1.85-1.93 (m, 2H), 1.70-1.73 (m, 1H), 1.52 (s, 3H), 1.01-1.08 (m, 6H) ppm.

Example 330

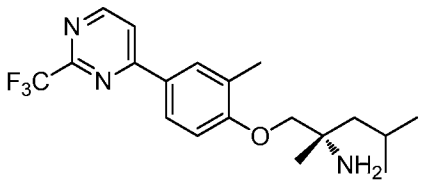
(*S*)-2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-amine





Part A: (S)-tert-butyl (2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate

A mixture of 4-chloro-2-(trifluoromethyl)pyrimidine (0.01 g, 0.055 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (prepared as described in Example 367, Part A) (0.029 g, 0.066 mmol), and KBr (6.52 mg, 0.055 mmol) in 1,4-dioxane (1 mL) was purged with nitrogen for15 min. $PdCl_2(dppf)$-CH_2Cl_2 adduct (4.47 mg, 5.48 μmol) was added, purged for a further 5 min then the reaction mixture was stirred at 80 °C microwave for 1.3 h. The reaction mixture was cooled to room temperature and diluted with THF (20 mL) and filtered through diatomaceous earth (Celite®). The bed was washed with excess of THF. Filtrate was concentrated under reduced pressure. The crude product was purified via silica gel chromatography (30-40% of ethyl acetate in pet ether) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate (0.015 g, 0.024 mmol, 44% yield) as a pale yellow oil. LCMS (ESI) *m/e* 468.3 $[(M+H)^+$, calcd for $C_{24}H_{33}F_3N_3O_3$, 468.24]; LC/MS retention time (method B); t_R = 1.29 min.



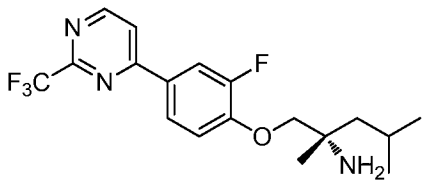
Part B: (S)-2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-amine

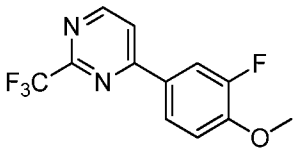
A solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate (0.015 g, 0.024 mmol) in MeOH (1.5 mL) cooled to 0 °C under a nitrogen atmosphere was stirred for 10 min. TFA (1.5 mL, 19.47 mmol) was added dropwise over a period of 1 min and

the mixture warmed to room temperature and allowed to stir for 4 h. The mixture was concentrated under reduced pressure. The residue was purified by prep HPLC (method B) to afford (*S*)-2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-amine, TFA (9.5 mg, 0.024 mmol, 84% yield) as a pale yellow solid. LCMS (ESI) m/e 368.0 [$(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$,368.18]; LC/MS retention time (method D); t_R = 1.83 min. LC/MS retention time (Method E); t_R = 1.47 min. ^{1}H NMR (400 MHz, DMSO-*d4*): δ 9.02 (d, *J* = 5.20 Hz, 1H), 8.33 (d, *J* = 5.60 Hz, 1H), 8.13-8.14 (m, 2H), 8.05 (bs, 2H), 7.19 (d, *J* = 8.40 Hz, 1H), 4.08-4.11 (m, 2H), 2.37 (s, 3H), 1.75-1.83 (m, 2H), 1.58-1.63 (m, 1H), 1.39 (s, 3H), 0.91-0.98 (m, 6H) ppm.

Example 331

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

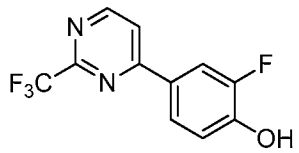




Part A: 4-(3-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)pyrimidine

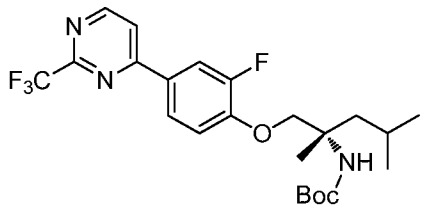
A mixture of 4-chloro-2-(trifluoromethyl)pyrimidine (0.06 g, 0.329 mmol), 2-(3-fluoro-4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.099 g, 0.394 mmol), Cs_2CO_3 (0.214 g, 0.657 mmol), and KBr (0.039 g, 0.329 mmol) in 1,4-dioxane (1.8 mL) was purged with nitrogen for 15 minutes. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.027 g, 0.033 mmol) was added and the mixture purged for a further 5 min. The reaction mixture was heated at 80 °C for 1.3 h. the reaction mixture was cool to room temperature and diluted with THF (20 mL) then filtered through diatomaceous earth (Celite®). The bed was washed with excess THF. The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography

(ethyl acetate and pet ether) to afford 4-(3-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)pyrimidine (0.115 g, 0.275 mmol, 53% yield) as a colorless semi-solid. LCMS (ESI) *m/e* 273.0 [$(M+H)^+$, calcd for $C_{12}H_9F_4N_2O$, 273.05]; LC/MS retention time (method B); t_R = 0.98 min.



Part B: 2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenol

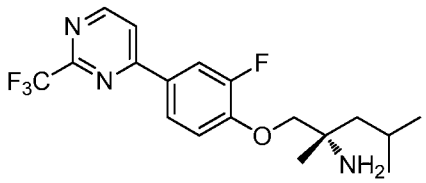
To a cooled solution of 4-(3-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)pyrimidine (0.01 g, 0.024 mmol) in DCM (1 mL) was added BBr_3 (4.52 µL, 0.048 mmol). The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was cooled to 0 °C and quenched with methanol and concentrated under reduced pressure. The residue was washed with diethyl ether (2 x 10 mL) the dried under high vacuum to afford 2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenol (0.006 g, 0.022 mmol, 93% yield) as a brown solid. The crude product was used as is for next step without further purification. LCMS (ESI) *m/e* 259.0 [$(M+H)^+$, calcd for $C_{11}H_7F_4N_2O$, 259.04]; LC/MS retention time (Method A1); t_R = 2.162.



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

A stirred suspension of 2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenol (0.04 g, 0.130 mmol) in DMF (2 mL) cooled to 0 °C was stirred for 10 min. K_2CO_3 (0.180 g, 1.301 mmol) was added and the mixture stirred at 0 °C for 5 min then at room temperature for 10 min. The reaction mixture was cooled to 0 °C and (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (0.038 g, 0.130 mmol) in DMF (2 mL) was added and the stirred for 10 min. The mixture was

then heated to 80 °C for 16 h. The mixture was cooled to room temperature and diluted with water (10 mL). the solution was extracted with ethyl acetate (4 x 20 mL). The combined the organic layers were washed with water (2x10 mL), then brine (2x5 mL). The combined the organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20-40 % ethyl acetate and pet ether) to afford (*S*)-*tert*-butyl (1-(2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.062 mmol, 40.8 % yield) as a yellow oil. LCMS (ESI) *m/e* 472.2 [(M+H)$^+$, calcd for $C_{23}H_{30}F_4N_3O_3$, 472.2]; LC/MS retention time (method B); t_R = 1.26 min.

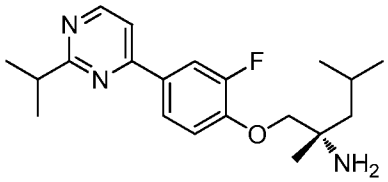


Part D: (S)-1-(2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-(2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4- dimethylpentan-2-yl)carbamate (0.05 g, 0.062 mmol) in MeOH (1.5 mL) cooled to 0 °C under nitrogen atmosphere was added TFA (1.5 mL, 19.47 mmol) dropwise over a period of 1 min. The mixture was then warmed to room temperature and allowed to stir for 4 h. The reaction mixture was concentrated under reduced pressure at lower temperature (28 °C). The crude material was purified by prep HPLC (method B) to afford (*S*)-1-(2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine, TFA (0.03 g, 0.059 mmol, 96% yield) as a pale yellow solid. LCMS (ESI) *m/e* 372.2 [(M+H)$^+$, calcd for $C_{18}H_{22}F_4N_3O$, 372.2]; LC/MS retention time (Method E); t_R = 1.42 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.95 (d, *J* = 5.20 Hz, 1H), 8.11-8.16 (m, 3H), 7.38 (t, *J* = 8.40 Hz, 1H), 4.29 (d, *J* = 10.40 Hz, 1H), 4.20 (d, *J* = 10.00 Hz, 1H), 1.84-1.91 (m, 2H), 1.67-1.72 (m, 1H), 1.51 (s, 3H), 0.96- 1.08 (m, 6H) ppm.

Example 337

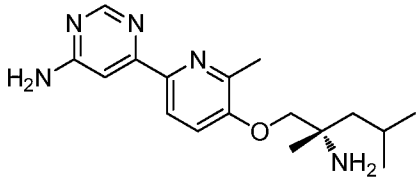
(*S*)-1-(2-fluoro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

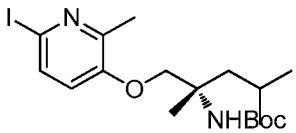


Prepared as described in Example 285 to afford (*S*)-1-(2-fluoro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine, TFA (1 mg, 0.017 mmol, 13% yield) as a pale yellow solid. LCMS (ESI) *m/e* 346.2 [(M+H)$^+$, calcd for $C_{20}H_{29}FN_3O$, 346.2]; LC/MS retention time (method D); t_R = 2.53. LC/MS retention time (Method E); t_R = 1.92 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.68 (d, *J* = 5.60 Hz, 1H), 8.07 (t, *J* = 10.00 Hz, 2H), 7.75 (d, *J* = 5.60 Hz, 1H), 7.33 (t, *J* = 8.40 Hz, 1H), 4.27 (d, *J* = 10.40 Hz, 1H), 4.18 (d, *J* = 10.40 Hz, 1H), 3.20-3.25 (m, 1H), 1.86-1.88 (m, 2H), 1.67-1.72 (m, 1H), 1.50 (s, 3H), 1.38-1.40 (m, 6H), 1.02-1.08 (m, 6H) ppm.

Example 343

(*S*)-6-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-4-amine

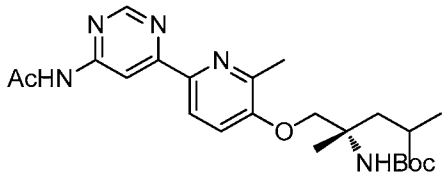




Part A. (S)-tert-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

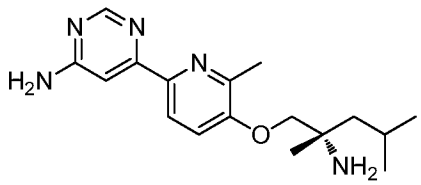
A mixture of 6-iodo-2-methylpyridin-3-ol (2.0 g, 8.51 mmol), K_2CO_3 (3.53 g, 25.5 mmol) and (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (2.75 g, 9.36 mmol) in DMF (25 mL) was heated to 80 °C overnight for 16 h. The mixture was cooled to room temperature and diluted with water (10 mL). The solution was extracted with ethyl acetate (4 x 20 mL). The combined the organic layers were washed with water (2x20 mL), then brine (2x20 mL). The combined the organic

layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (20-40 % ethyl acetate and pet ether) to afford (*S*)-*tert*-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (3.0 g, 6.36 mmol, 75% yield) as a pale semi-solid. ^{1}H NMR (400 MHz, *CHLOROFORM-d*): δ 7.43 (s, 1H), 6.78 - 6.85 (m, 1H), 4.46 - 4.53 (m, 1H), 4.08 - 4.17 (m, 1H), 3.92 - 3.99 (m, 1H), 2.44 (s, 3H), 1.74 - 1.88 (m, 2H), 1.56 (s, 3H), 1.47 - 1.53 (m, 1H), 1.34 - 1.44 (m, 9H), 0.97 (m, 6H) ppm.



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

A mixture of *N*-(6-chloropyrimidin-4-yl)acetamide (prepared as described in Example 278) (0.03 g, 0.175 mmol), (*S*)-*tert*-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.086 g, 0.192 mmol), hexamethylditin (0.054 mL, 0.262 mmol) and $Pd(Ph_3P)_4$ (0.020 g, 0.017 mmol) in 1,4-dioxane (3 mL) was heated under microwave at 150 °C for 90 min. After cooling, the reaction mixture was concentrated, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude (*S*)-*tert*-butyl (1-((6-(6-acetamidopyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.13 g, 0.121 mmol, 69% yield) as a yellowish semi-solid. LCMS (ES-API) *m/e* 458.3 [$(M+H)^+$, calcd for $C_{24}H_{36}N_5O_4$ 458.3]; LC/MS retention time (method B): t_R = 1.07 min.



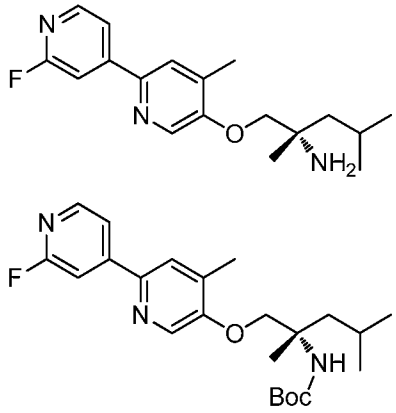
Part C. (S)-6-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-4-amine

To a stirred solution of (*S*)-*tert*-butyl (1-((6-(6-acetamidopyrimidin-4-yl)-2-

methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.1 g, 0.219 mmol) in MeOH (2 mL), cooled to 0 °C, was added 4N HCl in 1,4-dioxane (0.546 mL, 2.185 mmol) and the mixture stirred for 1 h. The reaction mixture was concentrated under reduced pressure to afford crude (*S*)-6-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-4-amine (0.02 g, 0.062 mmol, 28% yield) as a yellow solid. LCMS (ESI) *m/e* 316.3 $[(M+H)^+$, calcd for $C_{17}H_{26}N_5O$ 316.2; LCMS retention time (method F): t_R = 0.92 min. ^1H (400 MHz, *DMSO-d6*): δ 8.59 (s, 1H), 8.13-8.15 (br. m, 3H), 7.62 (d, *J* = 8.40 Hz, 1H), 7.35 (s, 1H), 4.12-4.19 (m, 2H), 2.59 (s, 3H), 1.74-1.86 (m, 2H), 1.60-1.65 (m, 1H), 1.41 (s, 3H), 0.94-0.99 (m, 6H) ppm.

Example 344

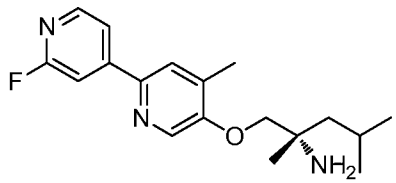
(*S*)-1-((2'-fluoro-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



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

A mixture of (2-fluoropyridin-4-yl)boronic acid (0.02 g, 0.142 mmol), (*S*)-*tert*-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (prepared in similar fashion as described in Example 226) (0.051 g, 0.142 mmol), and Cs_2CO_3 (0.116 g, 0.355 mmol) in 1,4-dioxane (1 mL) and water (0.2 mL). The mixture was purged with nitrogen for 15 min. $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.012 g, 0.014 mmol) was added and the mixture purged for a further 5 min then reaction mixture was heated to 100 °C for 14 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL) and filtered through diatomaceous earth (Celite®). The bed was washed with 20 mL of ethyl

acetate. The filtrate was concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-((2'-fluoro-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.089 mmol, 62% yield) as a yellow semi-solid. LCMS (ESI) *m/e* 418.7 [(M+H)$^+$, calcd for $C_{23}H_{33}FN_3O_3$, 418.2]; LC/MS retention time (method B); t_R = 1.18 min.

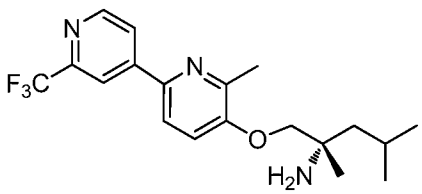


Part B: (S)-1-((2'-fluoro-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-((2'-fluoro-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.089 mmol) in MeOH (2 mL), cooled to 0 °C, was added 4N HCl in 1,4-dioxane (0.546 mL, 2.185 mmol) and the mixture stirred for 1 h. The reaction mixture was concentrated under reduced pressure and was purified by prep HPLC (method B) to afford (*S*)-1-((2'-fluoro-4-methyl-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine, TFA (13 mg, 0.089 mmol, 30% yield) as a pale yellow solid. LCMS (ESI) *m/e* 318.2 [(M+H)$^+$, calcd for $C_{18}H_{25}FN_3O$, 318.2]; LC/MS retention time (method D); t_R = 2.27. LC/MS retention time (Method E); t_R = 2.02 min. ^{1}H NMR (400MHz, METHANOL-d$_4$) δ 8.39 (s, 1H), 8.27 (d, *J*=5.0 Hz, 1H), 7.94 (s, 1H), 7.89 (td, *J*=1.5, 5.5 Hz, 1H), 7.66 (s, 1H), 4.34 - 4.23 (m, 2H), 2.45 (s, 3H), 1.93 - 1.83 (m, 2H), 1.74 - 1.68 (m, 1H), 1.53 (s, 3H), 1.09 - 1.00 (m, 6H) ppm.

Example 348

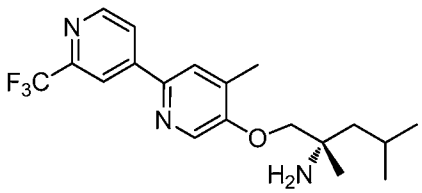
(*S*)-2,4-dimethyl-1-((6-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine



Prepared as described in Example 343. The crude material was purified by prep HPLC (method B) to afford (*S*)-2,4-dimethyl-1-((6-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine, 2 TFA (0.040 g, 0.065 mmol, 75 %) as a pale yellow solid. LCMS (ESI) *m/e* 368.3 $[(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$ 368.2]; LC/MS retention time (method H): t_R = 1.75 min; LC/MS retention time (method I): t_R = 1.32 min. ^{1}H NMR (400 MHz, MeOD): δ 8.76 (d, *J*=5.02 Hz, 1 H) 8.45 (d, *J*=1.00 Hz, 1 H) 8.23 (dd, *J*=5.02, 1.51 Hz, 1 H) 7.97 - 8.01 (m, 1 H) 7.53 (d, *J*=8.53 Hz, 1 H) 4.15 - 4.26 (m, 2 H) 2.65 (s, 3 H) 1.83 - 1.95 (m, 2 H) 1.69 - 1.78 (m, 1 H) 1.55 (s, 3 H) 1.01 - 1.11 (m, 6 H) ppm.

Example 349

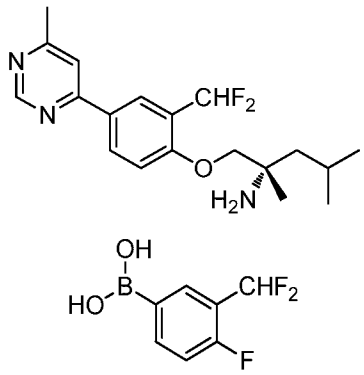
(*S*)-2,4-dimethyl-1-((4-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine



Prepared as described in Example 343. The crude material was purified by prep HPLC (method B) to (*S*)-2,4-dimethyl-1-((4-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine, 2 TFA (0.042 g, 0.071 mmol, 49% yield for the last step) as a pale yellow solid. LCMS (ESI) *m/e* 368.3 $[(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$ 368.2]; LC/MS retention time (method H): t_R = 1.68 min; LC/MS retention time (method I): t_R = 1.30 min. ^{1}H NMR (400 MHz, MeOD): δ 8.78 (d, *J*=5.02 Hz, 1 H) 8.44 (s, 2 H) 8.22 (dd, *J*=5.02, 1.51 Hz, 1H) 8.03 (s, 1H) 4.32 - 4.36 (m, 1H) 4.24 - 4.29 (m, 1H) 2.47 (s, 3H) 1.85 - 1.94 (m, 2H) 1.69 - 1.76 (m, 1H) 1.54 (s, 3H) 1.01 - 1.10 (m, 6H) ppm.

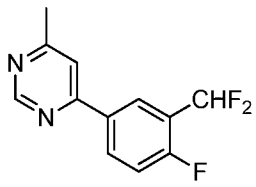
Example 350

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



Part A. (3-(difluoromethyl)-4-fluorophenyl)boronic acid

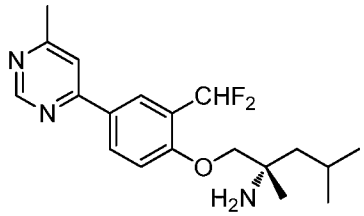
A solution of 4-bromo-2-(difluoromethyl)-1-fluorobenzene (1.2 g, 5.33 mmol), bis(pinacolato)diboron (1.490 g, 5.87 mmol) and potassium acetate (1.570 g, 16.00 mmol) in 1,4-dioxane (20 mL) was flushed with nitrogen. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.218 g, 0.267 mmol) was added and the reaction mixture was heated at 90 °C overnight. The reaction mixture was then filtered through diatomaceous earth (Celite®) and washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel chromatography (0-25% EtOAc in hexanes) to afford (3-(difluoromethyl)-4-fluorophenyl)boronic acid (1.2 g, 4.17 mmol, 78% yield). ^{1}H NMR (400 MHz, *CDCl3*): δ 8.04 (m, 1H), 7.90 (m, 1H), 7.11 (m, 1H), 6.87 (t, J = 15.2 Hz, 1H) ppm.



Part B. 4-(3-(difluoromethyl)-4-fluorophenyl)-6-methylpyrimidine

A solution of 2-(3-(difluoromethyl)-4-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.085 g, 0.311 mmol), 4-chloro-6-methylpyrimidine (0.04 g, 0.311 mmol) and potassium phosphate, dibasic (0.778 mL, 0.778 mmol) in 1,4-dioxane (3 mL) was purged with N_2 and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.025 g, 0.031 mmol) was added. The reaction mixture was purged with N_2 for 30 min and heated at 80 °C for 3 h. The reaction mixture was then filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford 4-(3-(difluoromethyl)-4-fluorophenyl)-

6-methylpyrimidine (0.1 g, 0.252 mmol, 81% yield) which was carried forward without further purification. LCMS (ESI) *m/e* 239.0 [(M+H)$^+$, calcd for $C_{12}H_{10}F_3N_2$ 239.1]; LC/MS retention time (Method G): t_R = 2.37 min.

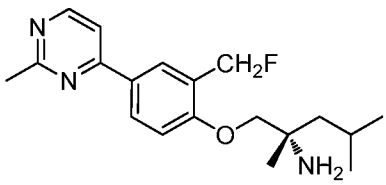


Part C. (S)-1-(2-(difluoromethyl)-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

A solution of 4-(3-(difluoromethyl)-4-fluorophenyl)-6-methylpyrimidine (0.1 g, 0.420 mmol), (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.055 g, 0.420 mmol) and KOtBu (1.259 mL, 1.259 mmol) in tetrahydrofuran (3 mL) was stirred at room temperature overnight. The reaction mixture filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (20 mL). The organic layer was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-1-(2-(difluoromethyl)-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (0.01 g, 0.028 mmol, 7% yield) as a pale yellow solid. LCMS (ESI) *m/e* 350.3 [(M+H)$^+$, calcd for $C_{19}H_{26}F_2N_3O$ 350.2]; LC/MS retention time (method H): t_R = 1.44 min; LC/MS retention time (method I): t_R = 1.09 min. ^{1}H NMR(400 MHz, methanol-*d4*): δ 9.03 (s, 1 H), 8.43 (s, 1 H), 8.36 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.91 (s, 1 H), 7.38-7.11 (m, 2H), 4.29 (d, *J*=10.4 Hz, 1 H), 4.20 (d, *J*=10.4 Hz, 1 H), 2.59 (s, 3 H), 1.88 (m, 2 H), 1.67 (m, 1 H), 1.49 (s, 3 H), 1.05 (m, 6 H) ppm.

Example 352

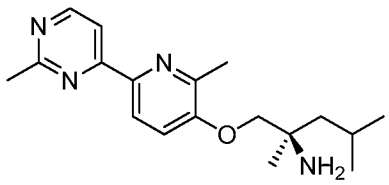
(*S*)-1-(2-(fluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

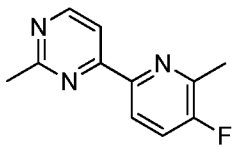


Prepared as described in Example 290. The crude final product was purified by prep HPLC (method B) (*S*)-1-(2-(fluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine, TFA (0.01 g, 0.028 mmol, 8% yield for the final two steps) as a pale yellow solid. LCMS (ESI) *m/e* 332.3 $[(M+H)^+$, calcd for $C_{19}H_{27}FN_3O$ 332.2]; LC/MS retention time (method H): t_R = 1.27 min; LC/MS retention time (method I): t_R = 0.93 min. ^{1}H NMR (400 MHz, MeOD): δ 8.66 - 8.71 (m, 1H), 8.25 - 8.34 (m, 2H), 7.84 - 7.91 (m, 1H), 7.26 (d, *J*=8.53 Hz, 1H), 5.63 - 5.74 (m, 1H), 5.51 - 5.62 (m, 1H), 4.14 - 4.30 (m, 2H), 2.79 (m, 3H), 1.80 - 1.93 (m, 2H), 1.64 - 1.75 (m, 1H), 1.51 (s, 3H), 0.97 - 1.10 (m, 6H) ppm.

Example 354

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

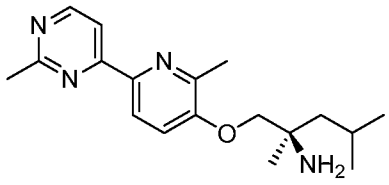




Part A: 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine

A solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), 6-bromo-3-fluoro-2-methylpyridine (148 mg, 0.778 mmol), and 1,1,1,2,2,2-hexamethyldistannane (255 mg, 0.778 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen gas for 10 min. $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas for another 10 min. The reaction mixture was heated in a microwave at 150 °C for 2 h. The reaction mixture was concentrated, then dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated from the filtrate, dried over Na_2SO_4, and concentrated under reduced pressure. The solid was purified by silica gel chromatography (0-40% EtOAc in petroleum ether) to afford the 4-(5-

fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (50 mg, 0.246 mmol, 32% yield) as a off-white solid. LCMS (ESI) *m/e* 204.2 [$(M+H)^+$, calcd for $C_{11}H_{11}FN_3$ 204.1]; LC/MS retention time (Method A1): t_R = 2.12 min.

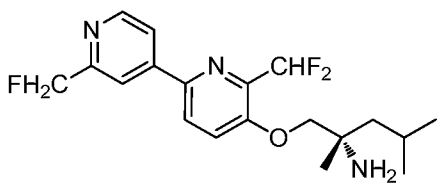


Part B: (R)-2,4-dimethyl-1-((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine

A solution of (*R*)-2-amino-2, 4-dimethylpentan-1-ol (0.021 g, 0.162 mmol) in THF (4 mL) was cooled to 0 °C. KOtBu (0.487 mL, 0.487 mmol) was added to the reaction mixture followed by slow addition of 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (0.033 g, 0.162 mmol). The reaction mixture was at stirred for 5 min at 0 °C then stirred at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature and quenched with water (20 mL). The reaction mixture was extracted with ethyl acetate (20 mL) and the organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford (*R*)-2,4-dimethyl-1-((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine (31 mg, 0.072 mmol, 44% yield) as a pale yellow solid. LCMS (ESI) *m/e* 315.3 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$ 315.2]; LC/MS retention time (method H): t_R = 1.26 min; LC/MS retention time (method I): t_R = 0.81 min. ^{1}H NMR(400 MHz, Methanol-d4): δ 8.71 (d, *J* = 5.60 Hz, 1H), 8.38 (d, *J* = 8.40 Hz, 1H), 8.18 (d, *J* = 5.60 Hz, 1H), 7.52 (d, *J* = 8.40 Hz, 1H), 4.14-4.21 (m, 2H), 2.76 (s, 3H), 2.64 (s, 3H), 1.85-1.91 (m, 2H), 1.71-1.75 (m, 1H), 1.51 (s, 3H), 1.02-1.09 (m, 6H) ppm.

Example 355

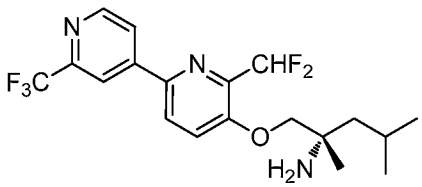
(*S*)-1-((6-(difluoromethyl)-2'-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine



Prepared as described in Example 324. The crude material was purified by prep HPLC (method B) to afford (*S*)-1-((6-(difluoromethyl)-2'-(fluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine, 2 TFA (0.023 g, 0.038 mmol, 29% yield for the last two steps) as a yellow solid. LCMS (ESI) *m/e* 368.3 $[(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O$ 368.2]; LC/MS retention time (method H): t_R = 1.48 min; LC/MS retention time (method I) : t_R = 1.06 min. ^{1}H NMR (400 MHz, MeOD): δ 8.64 (d, *J*=5.0 Hz, 1H), 8.28 - 8.18 (m, 2H), 8.07 (d, *J*=4.5 Hz, 1H), 7.80 (d, *J*=9.0 Hz, 1H), 7.29 - 7.00 (m, 1H), 5.60 (s, 1H), 5.48 (s, 1H), 4.33 - 4.21 (m, 2H), 1.90 - 1.82 (m, 2H), 1.74 - 1.66 (m, 1H), 1.52 (s, 3H), 1.10 - 1.03 (m, 6H) ppm.

Example 356

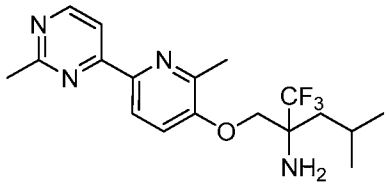
(*S*)-1-((6-(difluoromethyl)-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine

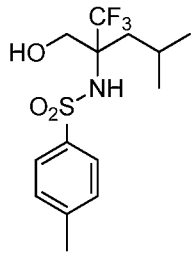


Prepared as described in Example 343. The crude material was purified by prep HPLC (method B) to afford (*S*)-1-((6-(difluoromethyl)-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine, TFA (0.040 g, 0.073 mmol, 73% yield for the last step) as a yellow solid. LCMS (ESI) *m/e* 404.3 $[(M+H)^+$, calcd for $C_{19}H_{23}F_5N_3O$ 404.2]; LC/MS retention time (method H): t_R = 1.82 min; LC/MS retention time (method I) : t_R = 1.47 min. ^{1}H NMR (400 MHz, MeOD): δ 8.81 (d, *J*=5.0 Hz, 1H), 8.49 (s, 1H), 8.35 - 8.30 (m, 2H), 7.83 (d, *J*=8.5 Hz, 1H), 7.31 - 7.02 (m, 1H), 4.35 - 4.23 (m, 2H), 1.91 - 1.82 (m, 2H), 1.75 - 1.68 (m, 1H), 1.53 (s, 3H), 1.09 - 0.99 (m, 6H) ppm.

Example 359

1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine



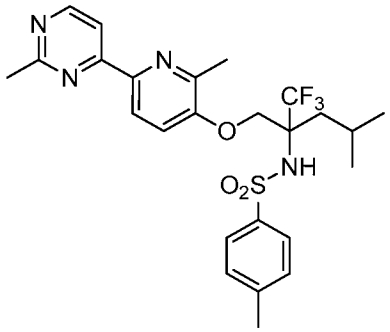


Part A: 4-methyl-N-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide

Racemic 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide (Prepared as described in Example 273, Parts A-D) (500 mg, 1.415 mmol)was resolved by chiral SFC. (Method: Column/dimensions: Chiralpak AD-H (250 X 30) mm, 5u; % CO_2: 85%; % Co solvent: 15%(0.25% DEA in Methanol); Total Flow: 100 g/min; Back Pressure: 100 bar; Temperature: 25°C; UV: 226 nm).

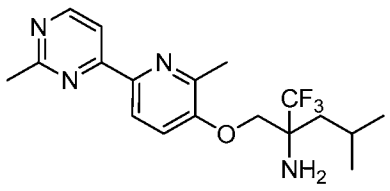
Isomer 1 was concentrated under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide (0.1 g, 0.268 mmol, 12% yield) as a yellow oil. LCMS (ESI) *m/e* 338.2 $[(M-H)^+$, calcd for $C_{14}H_{19}F_3NO_3S$, 338.1]; LC/MS retention time (Method G); t_R = 2.47 min

Isomer 2 was concentrated under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide (0.1 g, 0.224 mmol, 10% yield) as a yellow oil. LCMS (ESI) *m/e* 338.0 $[(M-H)^+$, calcd for $C_{14}H_{19}F_3NO_3S$, 338.3]; LC/MS retention time (Method G); t_R = 2.51 min.



Part B: 4-methyl-N-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide.

To a stirred solution of 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl)benzenesulfonamide, **isomer 1** (0.025 g, 0.074 mmol) in DMF (2 mL) cooled to 0 °C stirred for 10 min. NaH (8.86 mg, 0.221 mmol) in DMF(1 mL) was added and stirred for 5 min. 4-(5-Fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (prepared as described in Example 354) (0.015 g, 0.074 mmol) was added and the mixture was stirred at 80 °C for 5 h. The reaction mixture was cooled to 0 °C, quenched with ice cold water (10 mL) was extracted with ethyl acetate (2 x 20 mL). The combined the organic layers washed water (2x10 mL), then with brine (2x10 mL). The combined the organic layers were dried over sodium sulfate, concentrated under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide (0.04 g, 0.041 mmol, 56% yield) as a yellow semi solid which was carried forward without further purification. LCMS (ESI) m/e 523.6 [(M+H) +, calcd for $C_{25}H_{30}F_3N_4O_3S$, 523.2]; LC/MS retention time (method B); t_R = 0.99 min.



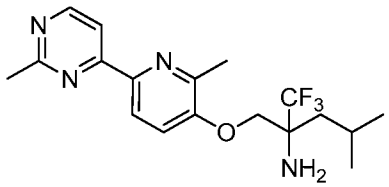
Part C: 1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine

A solution of 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide

(0.04 g, 0.077 mmol) in H_2SO_4 (98%) (1 mL, 18.76 mmol) was stirred at room temperature for 45 min. The reaction mixture was poured into cold saturated sodium bicarbonate solution and until pH~8-9. The reaction mixture was extracted with ethyl acetate (3x20 mL). The combined the organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford 1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine, TFA (0.002 g, 4.02 µmol, 5% yield) as a pale yellow solid. LCMS (ESI) *m/e* 369.2 $[(M+H)^+$, calcd for $C_{18}H_{24}F_3N_4O$ 369.3]; LC/MS retention time (method H): t_R = 1.98 min; LC/MS retention time (method I) : t_R = 1.21 min. ^{1}H NMR (400 MHz, MeOD): δ 8.74 (d, *J*=5.5 Hz, 1H), 8.41 (d, *J*=8.5 Hz, 1H), 8.24 (d, *J*=5.5 Hz, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 4.57 - 4.47 (m, 2H), 2.77 (s, 3H), 2.61 (s, 3H), 2.07 - 1.94 (m, 3H), 1.09-1.08 (m, 6H)

Example 360

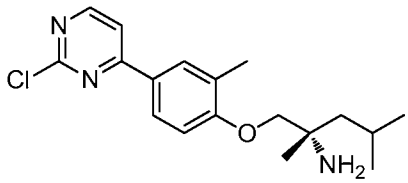
1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine

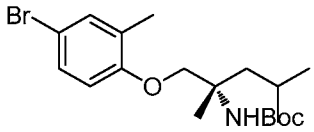


Prepared as described in Example 359 using 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide, **isomer 2** (0.038 g, 0.073 mmol) in Part A to afford 1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine, TFA (0.006 g, 0.016 mmol, 22% yield) as a pale yellow solid. LCMS (ESI) *m/e* 369.3 $[(M+H)^+$, calcd for $C_{18}H_{24}F_3N_4O$ 369.2]; LC/MS retention time (method H): t_R = 1.96 min; LC/MS retention time (method I) : t_R = 1.19 min. ^{1}H NMR (400 MHz, MeOD): δ 8.67 (d, *J*=5.5 Hz, 1H), 8.34 (d, *J*=8.5 Hz, 1H), 8.15 (d, *J*=4.5 Hz, 1H), 7.45 (d, *J*=8.5 Hz, 1H), 4.21 - 4.14 (m, 2H), 2.73 (s, 3H), 2.54 (s, 3H), 2.04 - 1.91 (m, 2H), 1.88 - 1.81 (m, 1H), 1.67-1.64 (m, 1H), 1.08 - 0.95 (m, 6H) ppm.

Example 367

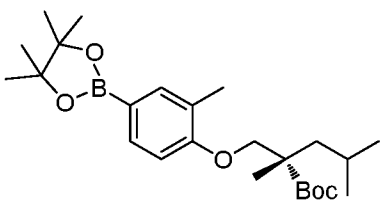
(*S*)-1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine





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

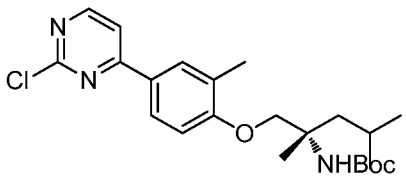
A mixture of 4-bromo-2-methylphenol (0.2 g, 1.069 mmol), K_2CO_3 (0.443 g, 3.21 mmol) and (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (0.376 g, 1.283 mmol) in DMF (5 mL) was heated at 80 °C overnight. The reaction mixture was cooled to 0 °C and quenched with aqueous ammonium chloride (50 mL). The reaction mixture was extracted with ethyl acetate (2x50 mL). The organic layer was washed with water (2x50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated to afford (*S*)-*tert*-butyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.3 g, 0.749 mmol, 70% yield). The material was carried forward without further purification. LCMS (ESI) *m/e* 346.0 $[(M+H-{}^tBu)^+$, calcd for $C_{19}H_{31}BrNO_3$ 400.1]; LC/MS retention time (method D): t_R = 3.27 min.



Part B. (S)-tert-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate

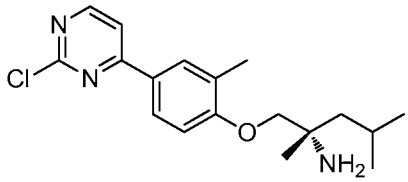
A mixture of (*S*)-*tert*-butyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.3 g, 0.749 mmol), bis(pinacolato)diboron (0.209 g,

0.824 mmol), potassium acetate (0.221 g, 2.248 mmol) and $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.031 g, 0.037 mmol) in 1,4-dioxane (25 mL) was heated at 90 °C overnight. The reaction mixture was filtered through celite and the celite bed was washed with ethyl acetate (100 mL). The organic layer was washed with water (50 mL). The aqueous layer was re-extracted with ethyl acetate (2x50 mL). The organic layer was collected, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford crude (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (0.2 g, 0.447 mmol, 60% yield). ^{1}H NMR (400 MHz, *CDCl*$_3$): δ 7.61 (t, *J* = 14.40 Hz, 2H), 6.81 (d, *J* = 10.80 Hz, 1H), 4.61 (bs, 1H), 4.08 (d, *J* = 11.60 Hz, 1H), 3.94 (d, *J* = 11.60 Hz, 1H), 2.24 (s, 3H), 1.76-1.84 (m, 2H), 1.61-1.66 (m, 1H), 1.51 (s, 3H), 1.33-1.43 (m, 12H), 0.95-0.98 (m, 6H) ppm.



Part C. (S)-tert-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 2,4-dichloropyrimidine (50 mg, 0.336 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (150 mg, 0.336 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (13.70 mg, 0.017 mmol) and 2M aq. potassium phosphate tribasic (0.503 mL, 1.007 mmol) in 1,4-dioxane (3 mL)-water (0.2 mL) was purged with nitrogen and heated at 100 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2x5 mL). The ethyl acetate layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (60 mg, 0.130 mmol, 39% yield) as a brown semi-solid which was carried forward without further purification. LCMS (ESI) *m/e* 434.2 [$(M+H)^+$, calcd for $C_{23}H_{33}ClN_3O_3$ 434.2]; LC/MS retention time (Method C): t_R = 1.54 min.

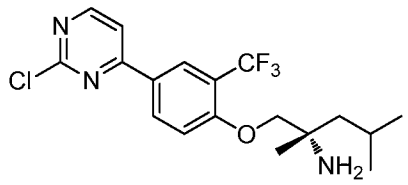


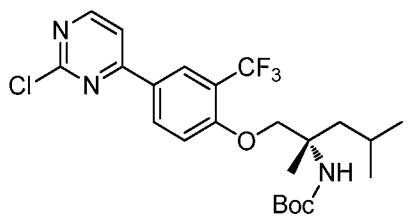
Part D. (S)-1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (25 mg, 0.058 mmol) in DCM at 0 °C was added 4N HCl in 1,4-dioxane (2 mL, 8.00 mmol) and the solution stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*S*)-1-(4-(2-chloropyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine (3 mg, 0.0872 mmol, 15% yield) as a pale yellow solid. LCMS (ESI) *m/e* 334.2 [$(M+H)^+$, calcd for $C_{18}H_{25}ClN_3O$ 334.2]; LC/MS retention time (method D): t_R = 2.38 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.60 (d, *J*=5.40 Hz, 1 H), 8.02 - 8.10 (m, 2H), 7.88 (d, *J*=5.46 Hz, 1H), 7.08 (d, *J*=8.47 Hz, 1H), 3.90 - 4.01 (m, 2H), 2.37 (s, 3H), 1.80 - 1.89 (m, 1H), 1.54 - 1.71 (m, 2H), 1.33 (s, 3H), 0.99 - 1.03 (m, 6H) ppm.

Example 370

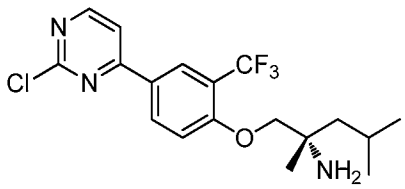
(*S*)-1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine





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

A mixture of 2,4-dichloropyrimidine (60 mg, 0.403 mmol), (*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 215, Parts A and B) (202 mg, 0.403 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.44 mg, 0.020 mmol), and 2N aq. potassium phosphate tribasic (0.604 mL, 1.208 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was purged with nitrogen and heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature, concentrated, diluted with water and extracted with ethyl acetate. The ethyl acetate layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (55 mg, 0.108 mmol, 27% yield) as a brown semi-solid. LCMS (ESI) *m/e* 488.2 [$(M+H)^+$, calcd for $C_{23}H_{30}ClF_3N_3O_3$ 488.2]; LC/MS retention time (method B): t_R = 1.29 min.

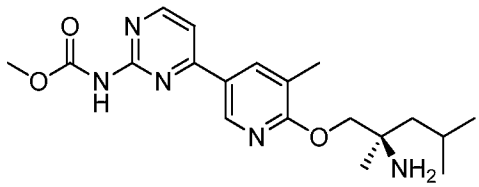


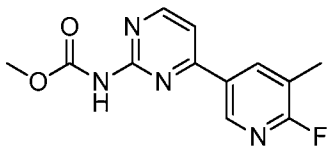
Part B: (S)-1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (10 mg, 0.020 mmol) in DCM (2 mL) at 0 °C, 4N HCl in 1,4-dioxane (2 mL, 8.00 mmol) was added and continued for 1 h at RT. The reaction mixture was concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*S*)-1-(4-(2-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (4 mg, 9.90 µmol, 48% yield) as an off-white solid. LCMS (ESI) *m/e* 388.2 [$(M+H)^+$, calcd for $C_{18}H_{22}ClF_3N_3O$ 388.1]; LC/MS retention time (method D): t_R = 2.28 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.71 (d, *J*=5.33 Hz, 1H), 8.45 - 8.53 (m, 2H), 7.99 (d, *J*=5.40 Hz, 1H), 7.42 (d, *J*=8.72 Hz, 1H), 4.12 - 4.21 (m, 2H), 1.70 - 1.91 (m, 2H), 1.58 - 1.67 (m, 1H), 1.41 (s, 3H), 1.03 (m, 6H) ppm.

Example 372

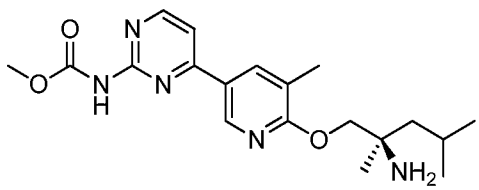
(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate





Part A: methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (65 mg, 0.347 mmol), 2-fluoro-3-methylpyridine-5-boronic acid (53.7 mg, 0.347 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (14.15 mg, 0.017 mmol) and Cs_2CO_3 (339 mg, 1.040 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was purged with nitrogen and heated at 100 °C for 6 h. The reaction mixture was diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (pet ether:ethyl acetate) to afford methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (60 mg, 0.169 mmol, 49% yield) as a brown solid. LCMS (ESI) *m/e* 263.0 $[(M+H)^+$, calcd for $C_{12}H_{12}FN_4O_2$ 263.1]; LC/MS retention time (Method C): t_R = 0.93 min.



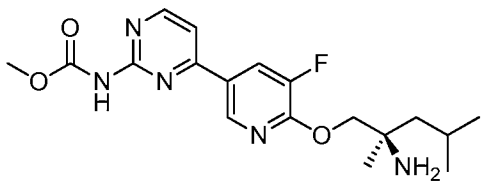
Part B: (R)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

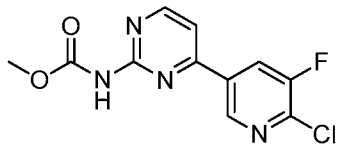
To a stirred solution of (*R*)-2-amino-2,4-dimethylpentan-1-ol (23.78 mg, 0.181 mmol) at 0 °C in DMF (3 mL), NaH (13.18 mg, 0.329 mmol) was added and

followed by methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (60 mg, 0.165 mmol). Mixture was heated at 60 °C for 12 h. The mixture was then was cooled to 0 °C, diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (11 mg, 0.028 mmol, 17% yield) as a yellowish solid. LCMS (ESI) *m/e* 374.2 [$(M+H)^+$, calcd for $C_{19}H_{28}N_5O_3$ 374.2]; LC/MS retention time (method D): t_R = 1.10 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.81 (dd, *J*=2.38, 0.56 Hz, 1H), 8.58 (d, *J*=5.33 Hz, 1H), 8.33 (dd, *J*=2.38, 0.88 Hz, 1H), 7.59 (d, *J*=5.40 Hz, 1H), 4.29 (s, 2H), 3.83 (s, 3H), 2.36 (s, 3H), 1.81 - 1.90 (m, 1H), 1.52 - 1.69 (m, 2H), 1.31 (s, 3H), 1.00 - 1.04 (m, 6H) ppm.

Example 373

(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate

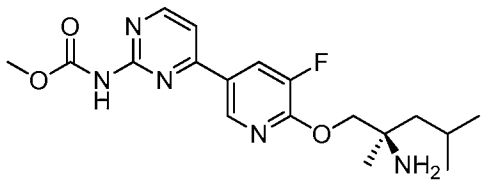




Part A: methyl (4-(6-chloro-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (65 mg, 0.347 mmol), 2-chloro-3-fluoropyridine-5-boronic acid (60.8 mg, 0.347 mmol), $PdCl_2$(dppf)-CH_2Cl_2-adduct (14.15 mg, 0.017 mmol) and Cs_2CO_3 (339 mg, 1.040 mmol) in 1,4-dioxane (1.5 mL)-water (0.1 mL) was purged with nitrogen and heated at 100 °C for 6 h. The reaction mixture was diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (50 mL).

The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (pet ether:ethyl acetate) to afford methyl (4-(6-chloro-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (50 mg, 0.092 mmol, 27% yield) as a brown solid. LCMS (ESI) *m/e* 283.0 $[(M+H)^+$, calcd for $C_{11}H_9ClFN_4O_2$ 283.0]; LC/MS retention time (Method C): t_R = 1.00 min.

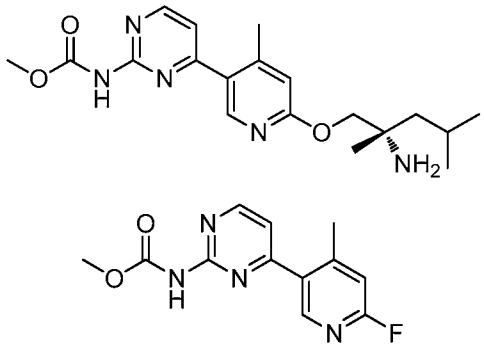


Part B: (R)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate

To a stirred solution of (*R*)-2-amino-2,4-dimethylpentan-1-ol (23.21 mg, 0.177 mmol) in DMF (2.5 mL) at 0 °C, NaH (14.15 mg, 0.354 mmol) was added and followed by methyl (4-(6-chloro-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (50 mg, 0.177 mmol) in 0.5 mL DMF. Mixture was heated at 60 °C for 12 h. The mixture was then was cooled to 0 °C, diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (2 mg, 0.0525 mmol, 3% yield) as a pale yellow solid. LCMS (ESI) *m/e* 378.2 $[(M+H)^+$, calcd for $C_{18}H_{25}FN_5O_3$ 378.2]; LC/MS retention time (method D): t_R = 1.77 min. ^{1}H NMR (400 MHz, *DMSO-d6*): δ 8.79 - 8.82 (m, 1H), 8.75 - 8.78 (m, 1H), 8.21 - 8.25 (m, 1H), 7.88 - 7.92 (m, 1H), 3.92 - 3.95 (m, 2H), 3.71 (s, 3H), 1.76 - 1.89 (m, 1H), 1.43 (dd, *J*=5.52, 2.82 Hz, 2H), 1.17 (s, 3H), 0.91 - 0.96 (m, 6H) ppm.

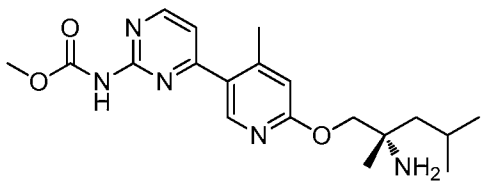
Example 374

(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate



Part A: methyl (4-(6-fluoro-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (75 mg, 0.400 mmol), 2-fluoro-4-methylpyridine-5-boronic acid (68.1 mg, 0.440 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.33 mg, 0.020 mmol) and Cs_2CO_3 (391 mg, 1.199 mmol) in 1,4-dioxane (2.5 mL)-water (0.1 mL) was purged with nitrogen and heated at 100 °C for 12h. The reaction mixture was diluted with ethyl acetate (25 mL) and filtered through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to afford methyl (4-(6-fluoro-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (75 mg, 0.117 mmol, 29% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 263.5 [$(M+H)^+$, calcd for $C_{12}H_{12}FN_4O_2$ 263.1]; LC/MS retention time (method B): t_R = 0.66 min.



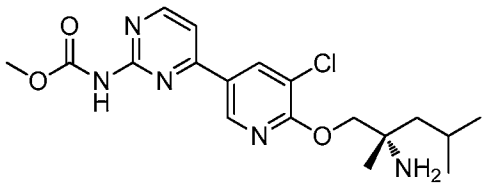
Part B: (S)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

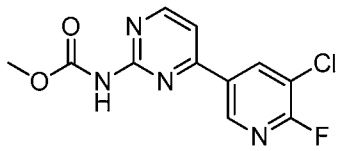
To a stirred solution of methyl (4-(6-fluoro-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (40 mg, 0.063 mmol) at 0 °C in DMF (3 mL), NaH (5.00 mg, 0.125 mmol) was added and followed by (*S*)-2-amino-2,4-dimethylpentan-1-ol (9.03 mg, 0.069 mmol). Mixture was allowed to warm to RT, and then heated at 60 °C for 3 h. The mixture was then was cooled to 0 °C, diluted with water (10 mL) and extracted

with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (5 mg, 0.013 mmol, 20% yield) as a pale yellow solid. LCMS (ESI) *m/e* 374.2 [$(M+H)^+$, calcd for $C_{19}H_{28}N_5O_3$ 374.2]; LC/MS retention time (method D): t_R = 1.64 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.65 (d, *J*=5.21 Hz, 1H), 8.34 (s, 1H), 7.32 (d, *J*=5.14 Hz, 1H), 6.92 (s, 1H), 4.38 - 4.51 (m, 2H), 3.82 (s, 3H), 2.56 (s, 3H), 1.78 - 1.94 (m, 2H), 1.65 - 1.71 (m, 1H), 1.49 (s, 3H), 1.05 (m, 6H) ppm.

Example 375

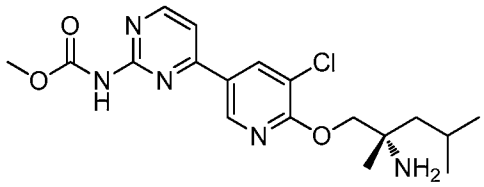
(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate





Part A: methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (75 mg, 0.400 mmol), (5-chloro-6-fluoropyridin-3-yl)boronic acid (77 mg, 0.440 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.33 mg, 0.020 mmol) and Cs_2CO_3 (391 mg, 1.199 mmol) in 1,4-dioxane (3.5 mL)-water (0.3 mL) was purged with nitrogen and heated at 100 °C for 12 h. The reaction mixture was diluted with ethyl acetate (25 mL) and filtered through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to afford a brown residue. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (50 mg, 0.087 mmol, 22% yield) as a brown solid. LCMS (ESI) *m/e* 283.0 [$(M+H)^+$, calcd for $C_{11}H_9ClFN_4O_2$ 283.0]; LC/MS retention time (Method C): t_R = 0.76 min.

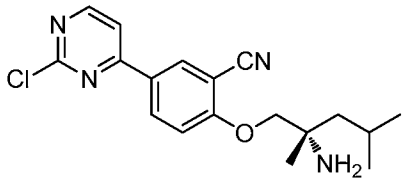


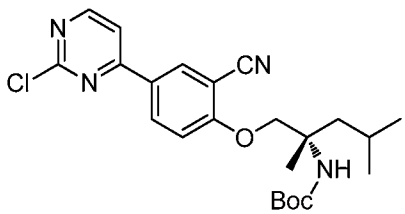
Part B: (S)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate

To a stirred solution of methyl (4-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate (40 mg, 0.069 mmol) at 0 °C in DMF (3 mL), NaH (5.55 mg, 0.139 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (10.01 mg, 0.076 mmol) were added and stirred at 60 °C for 3 h. The mixture was then was cooled to 0 °C, diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method B) to afford (*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate (10 mg, 0.024 mmol, 35% yield) as a pale yellow solid. LCMS (ESI) *m/e* 394.2 [$(M+H)^+$, calcd for $C_{18}H_{25}ClN_5O_3$ 394.2]; LC/MS retention time (method D): t_R = 1.92 min. ^1H NMR (400 MHz, *METHANOL-d4*): δ 8.93 (d, *J*=2.13 Hz, 1H), 8.67 (d, *J*=2.13 Hz, 1H), 8.63 (d, *J*=5.27 Hz, 1H), 7.64 (d, *J*=5.33 Hz, 1H), 4.60 (d, *J*=3.64 Hz, 2H), 3.84 (s, 3H), 1.85 - 1.96 (m, 2H), 1.68 - 1.77 (m, 1H), 1.53 (s, 3H), 1.07 (m, 6H) ppm.

Example 378

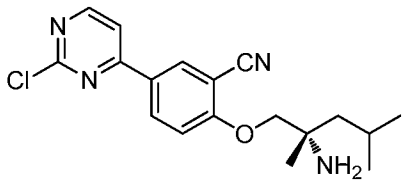
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-chloropyrimidin-4-yl)benzonitrile





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

A mixture of 2,4-dichloropyrimidine (70 mg, 0.470 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 (prepared as in Example 86, Parts A and B) (215 mg, 0.470 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (19.19 mg, 0.023 mmol), and potassium phosphate tribasic (216 mg, 1.410 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was purged with nitrogen and heated at 80 °C for 12h. The reaction mixture was diluted with ethyl acetate (25 mL) and filtered through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to afford a brown residue. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (130 mg, 0.216 mmol, 46% yield) as a brown semi-solid. LCMS (ESI) *m/e* 445.6 $[(M+H)^+$, calcd for $C_{23}H_{30}ClN_4O_3$ 445.2]; LC/MS retention time (method B): t_R = 1.25 min.



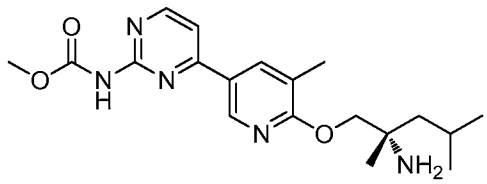
Part B: (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-chloropyrimidin-4-yl)benzonitrile

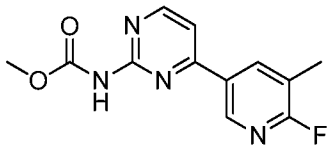
To a stirred solution of (*S*)-*tert*-butyl (1-(4-(2-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (25 mg, 0.056 mmol) in DCM at 0 °C was added 4N HCl in 1,4-dioxane (2 mL, 8.00 mmol) and the mixture was stirred for 1 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The EtOAc layer was collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method A) to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-chloropyrimidin-4-yl)benzonitrile (6 mg, 0.016 mmol, 28% yield) as a pale yellow solid. LCMS (ESI) *m/e* 345.2 $[(M+H)^+$, calcd for $C_{18}H_{22}ClN_4O$ 345.1]; LC/MS retention time (method D): t_R = 2.26 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.71 (d, *J*=5.33 Hz, 1H), 8.46 - 8.55 (m, 2H), 7.97 (d, *J*=5.33 Hz, 1H), 7.38 (d, *J*=8.91 Hz, 1H), 4.07 (d,

J=1.69 Hz, 2H), 1.82 - 1.92 (m, 1H), 1.53 - 1.69 (m, 2H), 1.32 (s, 3H), δ 0.98 - 1.05 (m, 6H) ppm.

Example 379

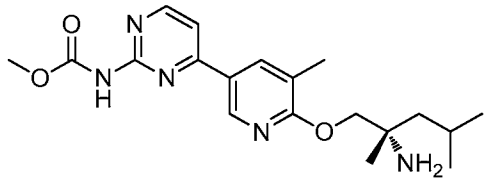
(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate





Part A. methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

To a stirred solution of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (75 mg, 0.400 mmol), 2-fluoro-3-methylpyridine-5-boronic acid (68.1 mg, 0.440 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (16.33 mg, 0.020 mmol) and Cs_2CO_3 (391 mg, 1.199 mmol) in 1,4-dioxane (3.5 mL)-water (0.3 mL) was purged with nitrogen and heated at 100 °C for 12 h. The reaction mixture was diluted with ethyl acetate (25 mL) and filtered through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to afford brown residue. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to afford methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (60 mg, 0.133 mmol, 33% yield) as a brown solid. LCMS (ESI) *m/e* 263.1 [$(M+H)^+$, calcd for $C_{12}H_{12}FN_4O_2$ 263.1]; LC/MS retention time (method B): t_R = 0.72 min.

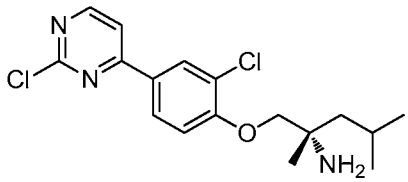


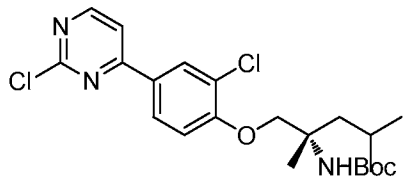
Part B. (S)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate

To a stirred solution of (*S*)-2-amino-2,4-dimethylpentan-1-ol (60 mg, 0.133 mmol) in DMF (3 mL) at 0 °C was added NaH (10.62 mg, 0.265 mmol) and the mixture stirred for 30 min. To the resulting mixture, methyl (4-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (19.15 mg, 0.146 mmol) was added and heated at 60 °C overnight. The reaction mixture was cooled to room temperature and was quenched with ice-water and diluted with ethyl acetate (20 mL). The organic layer was concentrated under reduced pressure to afford brown residue which was purified by reverse-phase column chromatography to obtain (*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate (3 mg, 0.0723 mmol, 5% yield) as a pale yellow solid. LCMS (ESI) *m/e* 374.2 $[(M+H)^+$, calcd for $C_{19}H_{28}N_5O_3$ 374.2]; LC/MS retention time (method D): t_R = 0.72 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.84 (d, *J*=1.88 Hz, 1H), 8.57 - 8.63 (m, 1H), 8.37 (d, *J*=2.32 Hz, 1H), 7.60 (d, *J*=5.27 Hz, 1H), 4.54 (s, 2H), 3.83 (s, 3H), 2.39 (s, 3H), 1.84 - 1.96 (m, 2H), 1.66 - 1.76 (m, 1H), 1.52 (s, 3H), 1.07 (m, 6H) ppm.

Example 382

(*S*)-1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

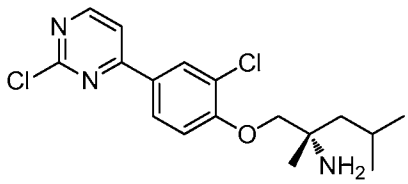




Part A. (S)-tert-butyl (1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 2,4-dichloropyrimidine (75 mg, 0.503 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as in Example 285, Part A) (236 mg, 0.503 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (20.56 mg, 0.025 mmol) and potassium

phosphate tribasic (232 mg, 1.510 mmol) in 1,4-dioxane (3 mL)-water (0.3 mL) was purged with nitrogen and heated at 80 °C for 3h. The reaction mixture was diluted with ethyl acetate (25 mL) and filtered through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to afford a brown residue. The residue was purified by silica gel chromatography (17% ethyl acetate in hexanes) to afford (*S*)-*tert*-butyl (1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (130 mg, 0.243 mmol, 48% yield) as a brown semi-solid. LCMS (ESI) *m/e* 454.1 [(M+H)$^+$, calcd for $C_{22}H_{30}Cl_2N_3O_3$ 454.2]; LC/MS retention time (Method C): t_R = 1.38 min.

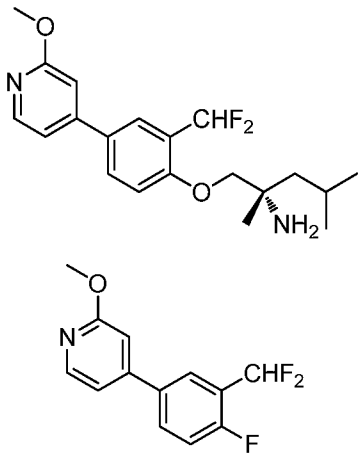


Part B. (S)-1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (15 mg, 0.033 mmol) in DCM at 0 °C 4N HCl in 1,4-dioxane (2 mL, 8.00 mmol) was added and stirred for 1 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2x25 mL). The EtOAc layer was collected, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude material was purified by prep HPLC (method A) to afford (*S*)-1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (1 mg, 0.0268 mmol, 8% yield) as a pale yellow solid. LCMS (ESI) *m/e* 354.0 [(M+H)$^+$, calcd for $C_{17}H_{22}Cl_2N_3O$, 354.1]; LC/MS retention time (method D): t_R = 2.61 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.70 (m, 1H), 8.33 (d, *J*=2.20 Hz, 1H), 8.16 - 8.23 (m, 1H), 7.95 (d, *J*=5.40 Hz, 1H), 7.34 (d, *J*=8.72 Hz, 1H), 4.25 (d, *J*=12.61 Hz, 2H), 1.85 - 2.02 (m, 2H), 1.68 - 1.79 (m, 1H), 1.54 (s, 3H), 1.03 - 1.10 (m, 6H) ppm.

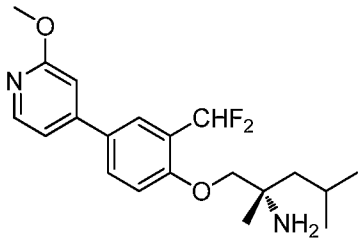
Example 383

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



Part A. 4-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxypyridine

A solution of (2-methoxypyridin-4-yl)boronic acid (75 mg, 0.490 mmol), 4-bromo-2-(difluoromethyl)-1-fluorobenzene (121 mg, 0.539 mmol), potassium phosphate tribasic (312 mg, 1.471 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 adduct (20.02 mg, 0.025 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was purged with nitrogen and heated to 90 °C for 4 h. The reaction mixture was diluted with ethyl acetate (10 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The residue was purified via silica gel chromatography (15% pet ether: ethyl acetate) to afford 4-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxypyridine (100 mg, 0.363 mmol, 74% yield) as a brown solid. LCMS (ESI) *m/e* 254.0 $[(M+H)^+$, calcd for $C_{13}H_{11}F_3NO$ 254.1]; LC/MS retention time (Method C): t_R = 1.02 min.



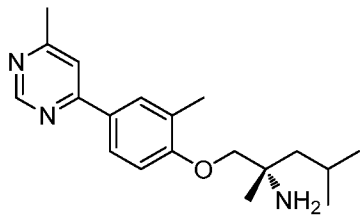
Part B. (S)-1-(2-(difluoromethyl)-4-(2-methoxypyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

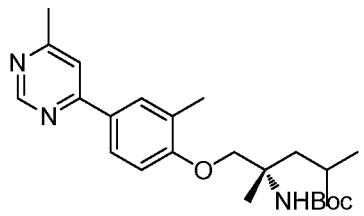
To a solution of 4-(3-(difluoromethyl)-4-fluorophenyl)-2-methoxypyridine (25 mg, 0.099 mmol) in THF (2 mL) at 0 °C was added (*S*)-2-amino-2,4-

dimethylpentan-1-ol (14.25 mg, 0.109 mmol) and 1 M potassium *tert*-butoxide in THF (0.148 mL, 0.148 mmol). The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1x10 mL), brine (1x10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown semi-solid. The crude material was purified by prep LC/MS (method B) to afford (*S*)-1-(2-(difluoromethyl)-4-(2-methoxypyridin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (6 mg, 0.016 mmol, 16% yield). LCMS (ESI) *m/e* 365.3 $[(M+H)^+$, calcd for $C_{20}H_{27}F_2N_2O_2$ 365.2]; LC/MS retention time (method H): t_R = 1.75 min. ^{1}H NMR(400 MHz, Methanol-d_4): δ 8.20 (dd, *J*=5.46, 0.56 Hz, 1 H), 7.88 - 7.95 (m, 2 H), 7.20 - 7.40 (m, 3 H), 7.03 - 7.12 (m, 1 H), 4.15 - 4.32 (m, 2 H), 3.98 (s, 3 H), 1.83 - 1.94 (m, 2 H), 1.71 (m, 1 H), 1.54 (br. s., 3 H), 1.01 - 1.09 (m, 6 H) ppm.

Example 384

(*S*)-2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-amine

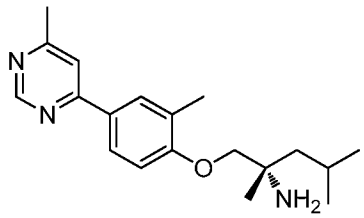




Part A. (S)-tert-butyl (2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate

A solution of 4-chloro-6-methylpyrimidine (15 mg, 0.117 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (prepared as described in Example 367, Part A) (52.2 mg, 0.117 mmol), potassium phosphate tribasic (74.2 mg, 0.350 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (4.76 mg, 5.83 μmol) in 1,4-dioxane (2 mL) and water

(0.2 mL) was purged with nitrogen and heated at 80 °C for 4 h. The reaction was diluted with ethyl acetate (20 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (0-20% EtOAc in petroleum ether) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate (30 mg, 0.039 mmol, 34% yield) as a brown semi-solid. LCMS (ESI) *m/e* 414.2 [$(M+H)^+$, calcd for $C_{24}H_{36}N_3O_3$ 414.2]; LC/MS retention time (Method C): t_R = 1.27 min.

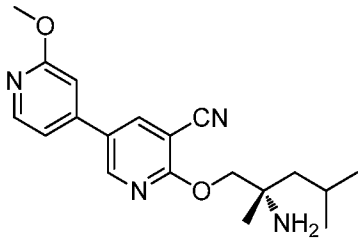


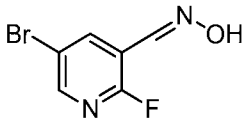
Part B. (S)-2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-amine

To a solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-yl)carbamate (30 mg, 0.073 mmol) in DCM at 0 °C was added 4 M HCl in 1,4-dioxane (2 mL, 8.00 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated and diluted with sodium bicarbonate solution (5 mL). The reaction mixture was extracted with ethyl acetate (2x50 mL). The ethyl acetate layer was washed with water (1x10 mL) and brine (1x10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a brown semi-solid. The crude material was purified by prep LC/MS (method B) to afford (*S*)-2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-amine (8 mg, 0.025 mmol, 35% yield). LCMS (ESI) *m/e* 314.3 [$(M+H)^+$, calcd for $C_{19}H_{28}N_3O$, 314.2]; LC/MS retention time (method H): t_R = 1.32 min. ^{1}H NMR (400 MHz, Methanol-*d*$_4$): δ 9.00 (d, *J*=1.19 Hz, 1 H), 8.03 - 8.08 (m, 2 H), 7.87 (s, 1 H), 7.14 (d, *J*=9.04 Hz, 1 H), 4.12 - 4.23 (m, 2 H), 2.60 (s, 3 H), 2.42 (s, 3 H), 1.82 - 1.96 (m, 2 H), 1.69 - 1.78 (m, 1 H), 1.54 (s, 3 H), 1.03 - 1.10 (m, 6 H) ppm.

Example 385

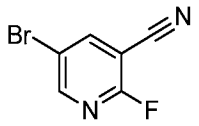
(*S*)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile





Part A. 5-bromo-2-fluoronicotinaldehyde oxime

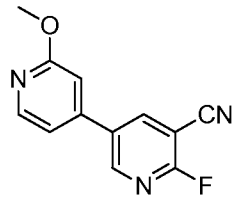
To a solution of hydroxylamine hydrochloride (1.506 g, 21.67 mmol) in ethanol (20 mL) and water (10 mL) was added 5-bromo-2-fluoronicotinaldehyde (3.4 g, 16.67 mmol). The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford 5-bromo-2-fluoronicotinaldehyde oxime (3.5 g, 15.98 mmol, 96% yield) as an off-white solid. LCMS (ESI) *m/e* 218.8 $[(M+H)^+$, calcd for $C_6H_5BrFN_2O$ 218.9]; LC/MS retention time (Method C): t_R = 0.78 min.



Part B. 5-bromo-2-fluoronicotinonitrile

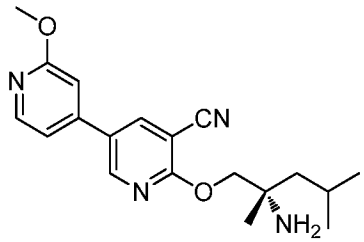
To a solution of 5-bromo-2-fluoronicotinaldehyde oxime (3.5 g, 15.98 mmol) in chloroform (40 mL) was slowly added $POCl_3$ (11.92 mL, 128 mmol) dropwise at room temperature. The reaction mixture was heated at 75 °C for 5 h. The reaction mixture was concentrated under reduced pressure. To the residue was added 10% sodium bicarbonate solution (10 mL) and the solution was extracted with ethyl acetate (2 x 250 mL). The ethyl acetate layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced

pressure to afford 5-bromo-2-fluoronicotinonitrile (3.1 g, 15.42 mmol, 97% yield) as a brown solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.92 (dd, J = 7.8, 2.4 Hz, 1 H), 8.75 (dd, J = 2.4 Hz, 1 H) ppm.



Part C. 6-fluoro-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile

A suspension of (2-methoxypyridin-4-yl)boronic acid (75 mg, 0.490 mmol), 5-bromo-2-fluoronicotinonitrile (108 mg, 0.539 mmol), potassium phosphate tribasic (312 mg, 1.471 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (20.02 mg, 0.025 mmol) in 1,4-dioxane (3 mL) and water (0.5 mL) was purged with nitrogen and heated to 90 °C for 4 h. The reaction mixture was diluted with ethyl acetate (10 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel chromatography (10-30% petroleum ether:ethyl acetate) to afford 6-fluoro-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile (40 mg, 0.150 mmol, 31% yield) as a brown solid. LCMS (ESI) *m/e* 230.5 [$(M+H)^+$, calcd for $C_{12}H_9FN_3O$ 230.1]; LC/MS retention time (method B): t_R = 0.83 min.



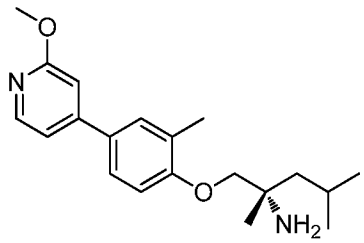
Part D. (S)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile

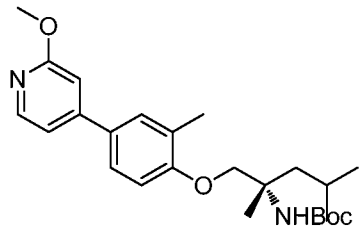
To a solution of 6-fluoro-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile (40 mg, 0.175 mmol) in THF (3 mL) at 0 °C was added 1 M potassium *tert*-butoxide in THF (0.262 mL, 0.262 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (25.2 mg, 0.192

mmol). The reaction mixture was allowed stir at room temperature for 2 h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The ethyl acetate layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown semi-solid. The crude material was purified by prep LC/MS (method B) to afford (*S*)-6-((2-amino-2,4-dimethylpentyl)oxy)-2'-methoxy-[3,4'-bipyridine]-5-carbonitrile (36 mg, 0.102 mmol, 58% yield). LCMS (ESI) *m/e* 341.2 $[(M+H)^+$, calcd for $C_{19}H_{25}N_4O_2$ 341.2]; LC/MS retention time (method H): t_R = 2.43 min. ^1H NMR (400 MHz, Methanol-*d4*): δ 8.82 (d, *J*=2.51 Hz, 1 H), 8.60 (d, *J*=2.51 Hz, 1 H), 8.26 (dd, *J*=5.46, 0.63 Hz, 1 H), 7.29 (dd, *J*=5.46, 1.63 Hz, 1 H), 7.15 (d, *J*=1.60 Hz, 1 H), 4.60 - 4.75 (m, 2 H), 3.97 - 4.03 (m, 3 H), 1.87 - 2.00 (m, 2 H), 1.67 - 1.78 (m, 1 H), 1.55 (s, 3 H), 1.07 - 1.11 (m, 6 H) ppm.

Example 386

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

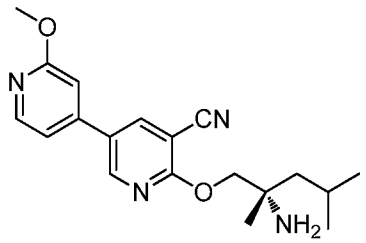




Part A. (S)-tert-butyl (1-(4-(2-methoxypyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

A solution of (2-methoxypyridin-4-yl)boronic acid (40 mg, 0.262 mmol), (*S*)-*tert*-butyl (1-(4-bromo-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 367) (105 mg, 0.262 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (10.68 mg, 0.013 mmol) and potassium phosphate tribasic (167 mg, 0.785

mmol) in 1,4-dioxane (3 mL) and water (0.2 mL) was purged with nitrogen and heated to 90 °C for 3 h. The reaction mixture was diluted with ethyl acetate (25 mL) and was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (10 mL) and the filtrate was concentrated under reduced pressure to afford a black residue which was purified via silica gel column (20% EtOAc in petroleum ether) to afford (*S*)-*tert*-butyl (1-(4-(2-methoxypyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (65 mg, 0.108 mmol, 41% yield) as a brown semi-solid. LCMS (ESI) *m/e* 429.7 [$(M+H)^+$, calcd for $C_{25}H_{37}N_2O_4$ 429.3]; LC/MS retention time (method B): t_R = 1.11 min.



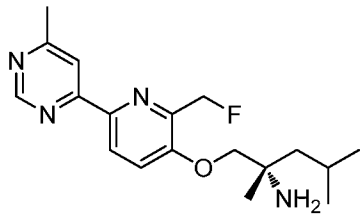
Part B. (S)-1-(4-(2-methoxypyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine

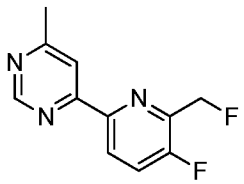
To a solution of (*S*)-*tert*-butyl (1-(4-(2-methoxypyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (65 mg, 0.152 mmol) in DCM at 0 °C was added 4 M HCl in 1,4-dioxane (5 mL, 20.00 mmol). The reaction mixture was allowed to stir for 1 h. The reaction mixture was concentrated and diluted with sodium bicarbonate solution (5 mL). The reaction mixture was extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 10 mL), and sat NaCl (1 x 10 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a brown semi-solid. The crude material was purified by prep LC/MS (method B) to afford (*S*)-1-(4-(2-methoxypyridin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine(29 mg, 0.086 mmol, 57% yield) as a pale yellow semi-solid. LCMS (ESI) *m/e* 329.3 [$(M+H)^+$, calcd for $C_{20}H_{29}N_2O_2$ 329.2]; LC/MS retention time (method H): t_R = 1.69 min. ^{1}H NMR (400 MHz, Methanol-d4): δ 8.18 (dd, *J*=5.77, 0.56 Hz, 1 H), 7.62 - 7.73 (m, 2 H), 7.37 (dd, *J*=5.77, 1.63 Hz, 1 H), 7.21 (s, 1 H), 7.12 (d, *J*=9.29 Hz, 1 H), 4.10 - 4.24 (m, 2 H),

4.05 (s, 3 H), 2.41 (s, 3 H), 1.83 - 1.95 (m, 2 H), 1.68 - 1.76 (m, 1 H), 1.54 (s, 3 H), 1.02 - 1.10 (m, 6 H) ppm.

Example 387

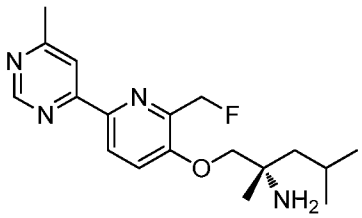
(*S*)-1-((2-(fluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine





Part A. 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-6-methylpyrimidine

A solution of 4-chloro-6-methylpyrimidine (100 mg, 0.778 mmol), hexamethylditin (129 µl, 0.622 mmol), tetrakis(triphenylphosphine)palladium (0) (44.9 mg, 0.039 mmol) and 6-bromo-3-fluoro-2-(fluoromethyl)pyridine (prepared as described in Example 279) (113 mg, 0.544 mmol) in 1,4-dioxane was purged with nitrogen and irradiated in a microwave at 120 °C for 1 h. The reaction mixture was diluted with ethyl acetate (10 mL) and the black suspension was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford a black residue which was purified by silica gel chromatography (5-20% EtOAc in petroleum ether) to afford 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-6-methylpyrimidine (90 mg, 0.224 mmol, 29% yield) as a brown semi-solid. LCMS (ESI) *m/e* 222.5 [$(M+H)^+$, calcd for $C_{11}H_{10}F_2N_3$ 222.1]; LC/MS retention time (method B): t_R = 0.77 min.

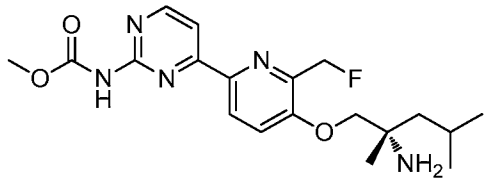


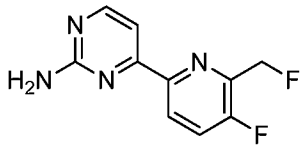
Part B. (S)-1-((2-(fluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

To a solution of 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)-6-methylpyrimidine (90 mg, 0.224 mmol) in THF (3 mL) at 0 °C was added 1 M potassium *tert*-butoxide in THF (0.336 mL, 0.336 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol(32.3 mg, 0.246 mmol). The reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 10 mL) and brine (1 x 10 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure to give a brown semi-solid. The crude material was purified by preparative LC/MS (method B) to afford (*S*)-1-((2-(fluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (30 mg, 0.089 mmol, 40% yield) as a pale yellow solid. LCMS (ESI) *m/e* 333.3 $[(M+H)^+$, calcd for $C_{18}H_{26}FN_4O$ 333.2]; LC/MS retention time (method I): t_R = 0.99 min. ^{1}H NMR (400 MHz, Methanol-d_4): δ 9.05 - 9.12 (m, 1 H), 8.56 - 8.62 (m, 1 H), 8.30 - 8.39 (m, 1 H), 7.69 - 7.78 (m, 1 H), 5.58 - 5.84 (m, 2 H), 4.22 - 4.36 (m, 2 H), 2.65 (s, 3 H), 1.86 - 1.98 (m, 2 H), 1.70 - 1.78 (m, 1 H), 1.55 (s, 3 H), 1.02 - 1.11 (m, 6 H) ppm.

Example 388

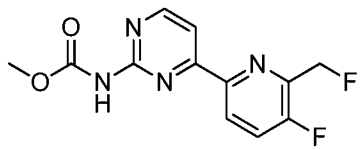
(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate





Part A. 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-amine

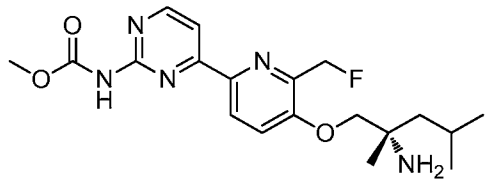
A solution of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (200 mg, 1.066 mmol), 6-bromo-3-fluoro-2-(fluoromethyl)pyridine (prepared as described in Example 279) (133 mg, 0.640 mmol), tetrakis(triphenylphosphine)palladium (0) (123 mg, 0.107 mmol) and bis(tributyltin) (619 mg, 1.07 mmol) in 1,4-dioxane (1.5 mL) was purged with nitrogen and irradiated in a microwave at 150 °C for 1.5 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (25 mL). The black suspension was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford black residue which was purified via silica gel chromatography (0-10% MeOH in DCM) to afford 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-amine (120 mg, 0.162 mmol, 15% yield) as a pale yellow solid. LCMS (ESI) *m/e* 223.0 [$(M+H)^+$, calcd for $C_{10}H_9F_2N_4$ 223.1]; LC/MS retention time (Method C): t_R = 0.72 min.



Part B. methyl (4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate

To a solution of 4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-amine (120 mg, 0.162 mmol) in chloroform (2.5 mL) and pyridine (2.5 mL) at 0 °C was added DMAP (1.979 mg, 0.016 mmol) and methyl chloroformate (0.063 mL, 0.810 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 20 mL), brine (1 x 20 mL), dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (10-40% EtOAc in petroleum ether) to afford methyl (4-(5-fluoro-6-(fluoromethyl)pyridin-2-

yl)pyrimidin-2-yl)carbamate (22 mg, 0.071 mmol, 44% yield) as an off-white solid. LCMS (ESI) *m/e* 281.1 [$(M+H)^+$, calcd for $C_{12}H_{11}F_2N_4O_2$ 281.1]; LC/MS retention time (Method C): t_R = 0.76 min.

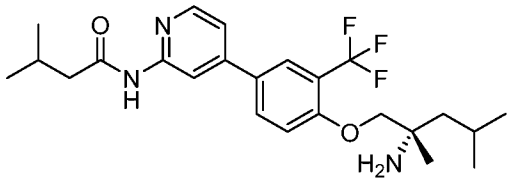


Part C. (S)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate

To a solution of methyl (4-(5-fluoro-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate (22 mg, 0.079 mmol) in DMF (3 mL) at 0 °C was added NaH (6.28 mg, 0.157 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (11.33 mg, 0.086 mmol). The reaction mixture was heated to 60 °C overnight. The reaction mixture was cooled to 0 °C, diluted with water (5 mL) and extracted with ethyl acetate (2 x 50 mL). The ethyl acetate layer was washed with water (1 x 10 mL), and saturated NaCl (1 x 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method C) to afford (*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate (4 mg, 9.50 µmol, 12% yield) as a yellow solid. LCMS (ESI) *m/e* 392.3 [$(M+H)^+$, calcd for $C_{19}H_{27}FN_5O_3$ 392.2]; LC/MS retention time (method H): t_R = 1.25 min; LC/MS retention time (method I): t_R = 0.83 min. ^{1}H NMR (400 MHz, Methanol-d_4): δ 8.67 (d, *J*=5.27 Hz, 1 H), 8.59 (dd, *J*=8.72, 1.63 Hz, 1 H), 8.04 (d, *J*=5.21 Hz, 1 H), 7.67 (d, *J*=8.72 Hz, 1 H), 5.72 (d, *J*=11.11 Hz, 1 H), 5.60 (d, *J*=11.04 Hz, 1 H), 4.09 - 4.21 (m, 2 H), 3.84 (s, 3 H), 1.83 - 1.92 (m, 1 H), 1.74 - 1.82 (m, 1 H), 1.61 - 1.69 (m, 1 H), 1.43 (s, 3 H), 1.02 - 1.07 (m, 6 H) ppm.

Example 395

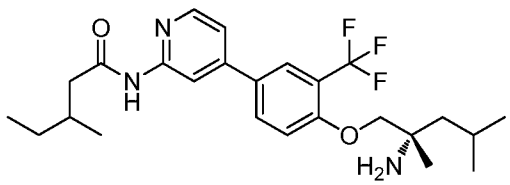
(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-3-methylbutanamide



To a flask containing (*S*)-*tert*-butyl (1-(4-(2-aminopyridin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (20 mg, 0.043 mmol) (prepared as described in Example 297) was added 3-methylbutanoic acid (0.051 mmol, 1.2 equiv.), HATU (24.40 mg, 0.064 mmol), DIPEA (0.022 mL, 0.128 mmol) and DMF (1 mL). The reaction mixture was heated at 60 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. To the residue at 0 °C was added 30% TFA in DCM (1 mL) and the mixture stirred for 30 min. The solvent was removed and the crude material was purified by reverse phase prep HPLC (Method E) to afford (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-3-methylbutanamide (6.0 mg, 0.013 mmol, 31% yield for two steps) as a pale yellow solid. LCMS (ESI) *m/e* 452.2 [$(M+H)^+$, calcd for $C_{24}H_{33}F_3N_3O_2$ 452.2]; LC/MS retention time (method H): t_R = 2.81 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.40 (d, *J*=1.0 Hz, 1H), 8.37 - 8.34 (m, 1H), 7.99 (dd, *J*=8.8, 2.3 Hz, 1H), 7.89 (d, *J*=2.0 Hz, 1H), 7.44 (dd, *J*=5.3, 1.5 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 3.94 - 3.86 (m, 2H), 2.34 - 2.28 (m, 2H), 2.09 (dquin, *J*=13.6, 6.8 Hz, 1H), 1.80 (dquin, *J*=12.7, 6.3 Hz, 1H), 1.47 - 1.37 (m, 2H), 1.15 (s, 3H), 0.97 - 0.88 (m, 12H) ppm.

Example 396

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

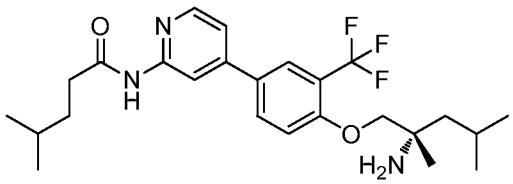


Prepared as described in Example 395 to afford *N*-(4-(4-(((*S*)-2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-3-methylpentanamide (6.0 mg, 0.013 mmol, 30% yield for two steps) as a pale yellow solid. LCMS (ESI)

m/e 466.2 [(M+H)$^+$, calcd for $C_{25}H_{35}F_3N_3O_2$ 466.2]; LC/MS retention time (method H): t_R = 2.98 min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 8.40 (d, *J*=1.0 Hz, 1H), 8.35 (d, *J*=5.3 Hz, 1H), 7.99 (dd, *J*=8.5, 2.3 Hz, 1H), 7.89 (d, *J*=2.0 Hz, 1H), 7.44 (dd, *J*=5.3, 1.8 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 3.92 - 3.85 (m, 2H), 2.43 - 2.38 (m, 1H), 2.28 - 2.21 (m, 1H), 1.94 - 1.75 (m, 2H), 1.46 - 1.31 (m, 3H), 1.26 - 1.17 (m, 1H), 1.14 (s, 3H), 0.94 - 0.85 (m, 12H) ppm.

Example 397

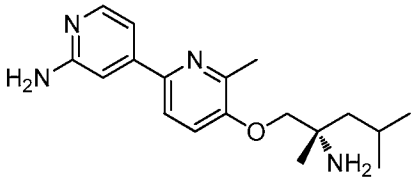
(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-4-methylpentanamide



Prepared as described in Example 395 to afford (*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-4-methylpentanamide (6.3 mg, 0.014 mmol, 32% yield for two steps) as a pale yellow solid. LCMS (ESI) *m/e* 466.2 [(M+H)$^+$, calcd for $C_{25}H_{35}F_3N_3O_2$ 466.2]; LC/MS retention time (method H): t_R = 3.01min. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.41 - 8.36 (m, 2H), 8.02 (dd, *J*=8.8, 2.3 Hz, 1H), 7.91 (d, *J*=2.0 Hz, 1H), 7.46 - 7.41 (m, 2H), 4.02 - 3.96 (m, 2H), 2.46 - 2.41 (m, 2H), 1.82 (dt, *J*=12.7, 6.1 Hz, 1H), 1.61 - 1.43 (m, 5H), 1.22 (s, 3H), 0.96 - 0.88 (m, 12H) ppm.

Example 422

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

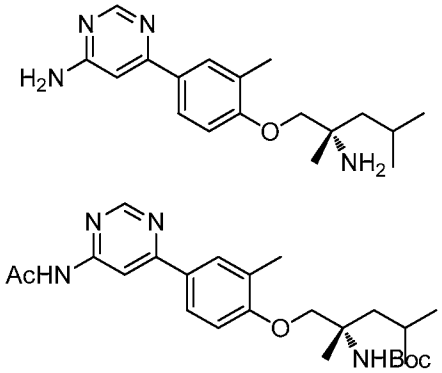


A solution of (*S*)-methyl (5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-yl)carbamate (prepared as described in Example 64) (0.025 g, 0.067 mmol) in ethanol (1 mL)-H_2O (1 mL), was treated with KOH (0.038 g, 0.671 mmol) and heated to reflux for 5 h. The reaction mixture was cooled to room

temperature and diluted with water (50 mL). The solution was extracted with dichloromethane (80 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method B) to afford (*S*)-5-((2-amino-2,4-dimethylpentyl)oxy)-6-methyl-[2,4'-bipyridin]-2'-amine (0.005 g, 0.016 mmol, 24% yield) as a yellow solid. LCMS (ESI) *m/e* 315.2 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$ 315.2]; LC/MS retention time (Method E): t_R = 0.71 min; LCMS retention time (method F): t_R = 0.97 min. ^1H NMR (400 MHz, *METHANOL-d4*): δ 7.93 (m, 2H), 7.69 (d, *J*=1.00 Hz, 1H), 7.51 - 7.57 (m, 2H), 4.15 - 4.29 (m, 2H), 2.65 (s, 3H), 1.84 - 1.96 (m, 2H), 1.73 (d, *J*=9.04 Hz, 1H), 1.55 (s, 3H), 1.00 - 1.13 (m, 6H) ppm.

Example 431

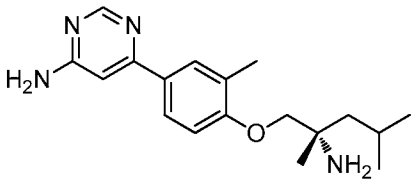
(*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-amine



Part A. (S)-tert-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of *N*-(6-chloropyrimidin-4-yl)acetamide (prepared as described in Example 278) (0.03 g, 0.175 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (prepared as described in Example 367, Part A) (0.056 g, 0.125 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (10.20 mg, 0.012 mmol) and Cs_2CO_3 (0.122 g, 0.375 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl(1-(4-(6-acetamidopyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-

yl)carbamate as a yellowish semi-solid. LCMS (ES-API) *m/e* 457.2 [(M+H)$^+$, calcd for $C_{25}H_{37}N_4O_4$, 457.3]; LC/MS retention time (method D): t_R = 2.45 min.

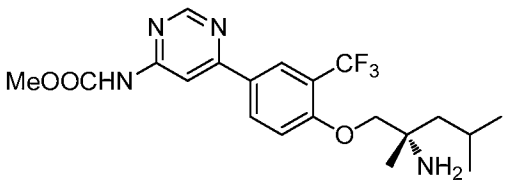


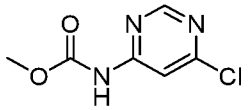
Part B. (S)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-amine

To a solution of (*S*)-*tert*-butyl (1-(4-(6-acetamidopyrimidin-4-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.110 mmol) in MeOH (3 mL), cooled to 0 °C, was added 4N HCl in 1,4-dioxane (0.274 mL, 1.095 mmol). The reaction mixture was stirred at RT for 1 h. The reaction mixture was concentrated under reduced pressure and was purified by prep HPLC (method B) to afford (*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-amine (0.016 g, 0.051 mmol, 46% yield) as a pale yellow solid. LCMS (ESI) *m/e* 315.2 [(M+H)$^+$, calcd for $C_{18}H_{26}N_4O$ 315.2]; LCMS retention time (method F): t_R = 1.08 min; LCMS retention time (method G): t_R = 0.73 min. ^{1}H NMR (400 MHz, *CD$_3$OD*): δ 8.60 (d, *J* = 0.80 Hz, 1H), 7.73-7.76 (m, 2H), 7.24 (d, *J* = 8.40 Hz, 1H), 6.96 (d, *J* = 0.80 Hz, 1H), 4.17-4.26 (m, 2H), 2.44 (s, 3H), 1.89-1.95 (m, 2H), 1.71-1.75 (m, 1H), 1.55 (s, 3H), 1.02-1.09 (m, 6H) ppm.

Example 432

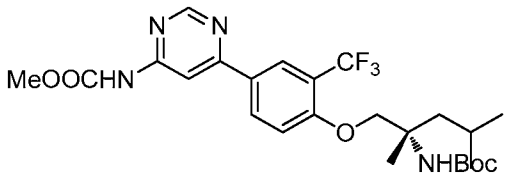
(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate





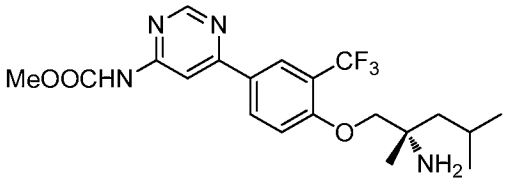
Part A. N-(6-chloropyrimidin-4-yl)acetamide

A mixture of 4,6-dichloropyrimidine (0.1 g, 0.671 mmol), methyl carbamate (0.050 g, 0.671 mmol), Cs_2CO_3 (0.437 g, 1.342 mmol), $PdOAc_2$ (6.03 mg, 0.027 mmol) and XANTPHOS (0.035 g, 0.060 mmol) in 1,4-dioxane (5 mL) was heated at 75 °C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (25 mL) and extracted with ethyl acetate (2x25 mL). The ethyl acetate layer was collected, washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (6-chloropyrimidin-4-yl)carbamate (0.08 g, 0.418 mmol, 62% yield) as a brown solid. LCMS (ESI) *m/e* 186.0 [$(M-H)^-$, calcd for $C_6H_5ClN_3O_2$ 186.0]; LC/MS retention time (method D): t_R = 1.26 min.



Part B. Boc-(S)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate

A mixture of methyl (6-chloropyrimidin-4-yl)carbamate (0.03 g, 0.160 mmol), (*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 215, Parts A and B) (0.057 g, 0.114 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (9.33 mg, 0.011 mmol) and Cs_2CO_3 (0.112 g, 0.343 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford Boc-(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate (0.1 g, 0.103 mmol, 90% yield) as a yellowish semi-solid. LCMS (ES-API) *m/e* 527.2 [$(M+H)^+$, calcd for $C_{25}H_{34}F_3N_4O_5$ 527.2]; LC/MS retention time (method D): t_R = 2.61 min.

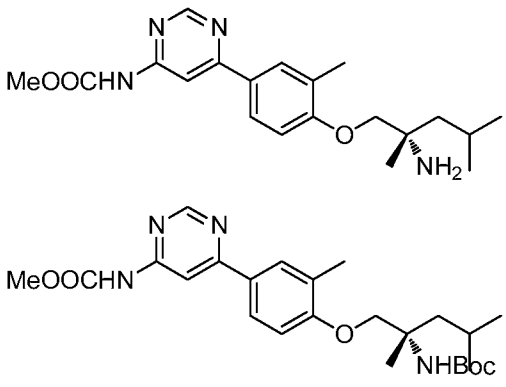


Part C. (S)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate

To a stirred solution of Boc-(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate (0.08 g, 0.082 mmol) in MeOH (2 mL) cooled to 0 °C was added 4N HCl in 1,4-dioxane (0.205 mL, 0.820 mmol) and the mixture stirred for 1 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate (0.020 g, 0.044 mmol, 54% yield) as a yellow solid. LCMS (ESI) *m/e* 427.2 [$(M+H)^+$, calcd for $C_{20}H_{25}F_3N_4O_3$ 427.2]; LCMS retention time (method F): t_R = 2.34 min; LCMS retention time (method G): t_R = 1.82 min. ^{1}H NMR (400 MHz, *DMSO-d6*): δ 8.88 (d, *J*=1.00 Hz, 1H), 8.31 - 8.38 (m, 3H), 7.43 (d, *J*=8.53 Hz, 1H), 3.95 (d, *J*=4.02 Hz, 2H), 3.76 (s, 3H), 1.76 - 1.87 (m, 1H), 1.44 (m, 2H), 1.13 - 1.20 (m, 3H), 0.88 - 0.97 (m, 6H) ppm.

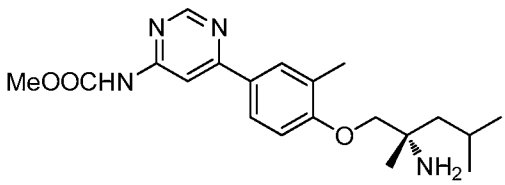
Example 433

(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate



Part A. Boc-(S)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate

A mixture of methyl (6-chloropyrimidin-4-yl)carbamate (prepared as described in Example 432) (0.05 g, 0.267 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (prepared as described in Example 367, Part A) (0.085 g, 0.190 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.016 g, 0.019 mmol) and Cs_2CO_3 (0.186 g, 0.571 mmol)) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (15 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford Boc-(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate (0.08 g, 0.113 mmol, 60% yield) as a yellowish semi-solid. LCMS (ES-API) *m/e* 471.2 [$(M-H)^-$, calcd for $C_{25}H_{35}N_4O_5$ 471.3]; LC/MS retention time (method D): t_R = 2.59 min.



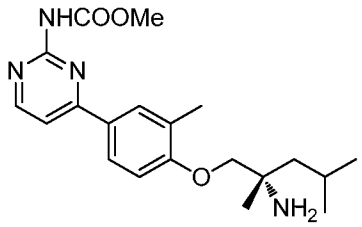
Part B. (S)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate

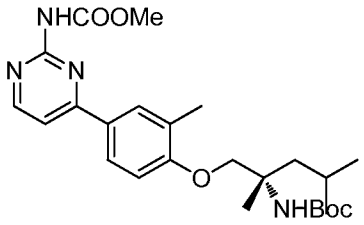
A solution of Boc-(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate (0.1 g, 0.142 mmol) in MeOH (2 mL) cooled to 0° C was added 4N HCl in 1,4-dioxane (0.35 mL, 1.42 mmol) and the mixture stirred for 3 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate (0.01 g, 0.026 mmol, 18% yield) as a yellow solid. LCMS (ESI) *m/e* 373.2 [$(M+H)^+$, calcd for $C_{20}H_{29}N_4O_3$ 373.2]; LCMS retention time (method F): t_R = 1.36 min; LCMS retention time (method G): t_R = 1.18 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ

8.75 (d, *J*=1.51 Hz, 1H), 8.35 (d, *J*=1.00 Hz, 1H), 7.91 (s, 2H), 7.08 (d, *J*=8.03 Hz, 1H), 3.98 (d, *J*=6.02 Hz, 2H), 3.85 (s, 3H), 2.39 (s, 3H), 1.81 - 1.88 (m, 1H), 1.54 - 1.76 (m, 2H), 1.37 (s, 3H), 1.03 (m, 6H) ppm.

Example 434

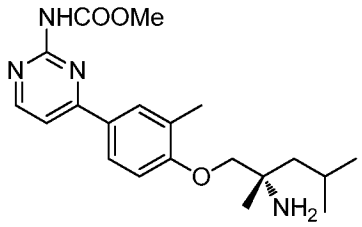
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate





Part A. Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (prepared as described in Example 304) (0.05 g, 0.267 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (prepared as described in Example 367, Part A) (0.119 g, 0.267 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.022 g, 0.027 mmol) and Cs_2CO_3 (0.261 g, 0.800 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate (0.13 g, 0.203 mmol, 76% yield) as a pale yellow semi-solid. LCMS (ESI) *m/e* 473.2 [$(M+H)^+$, calcd for $C_{25}H_{37}N_4O_5$ 473.3]; LC/MS retention time (method A1): t_R = 2.53 min.

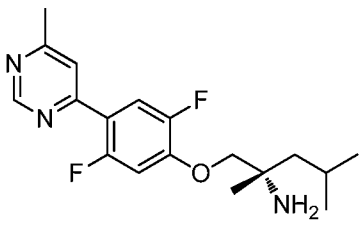


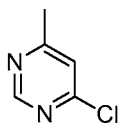
Part B. (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate

To a stirred solution of Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate (0.13 g, 0.275 mmol) in MeOH (2 mL) cooled to 0 °C was added 4N HCl in 1,4-dioxane (0.688 mL, 2.75 mmol) and the mixture stirred for 4 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate (0.035 g, 0.091 mmol, 33% yield) as a yellow solid. LCMS (ESI) *m/e* 373.2 [$(M+H)^+$, calcd for $C_{20}H_{29}N_4O_3$ 373.2]; LC/MS retention time (method D): t_R = 1.89 min. LCMS retention time (method G): t_R = 1.61 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.53 (d, *J* = 5.20 Hz, 1H), 8.05-8.07 (m, 2H), 7.56 (d, *J* = 5.20 Hz, 1H), 7.05 (d, *J* = 9.20 Hz, 1H), 3.91-3.94 (m, 2H), 3.83 (s, 3H), 2.37 (s, 3H), 1.84-1.87 (m, 1H), 1.56-1.70 (m, 2H), 1.33 (s, 3H), 1.00-1.04 (m, 6H) ppm.

Example 435

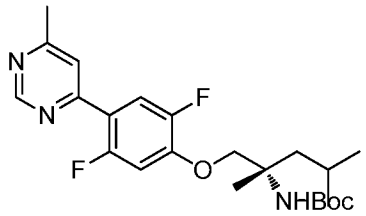
(*S*)-1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





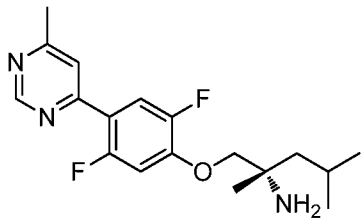
Part A. 4-chloro-6-methylpyrimidine

To a solution of 4,6-dichloropyrimidine (1.0 g, 6.71 mmol) in tetrahydrofuran (30 mL) was added 1-methyl-2-pyrrolidinone (3.2 mL, 6.71 mmol), iron(III) acetylacetonate (0.119 g, 0.336 mmol) and methylmagnesium bromide (2.237 mL, 6.71 mmol). The reaction mixture was stirred at RT for 3 h, then it was quenched with water and extracted with ethyl acetate (100 mL). The organic layer was separated out and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% ethyl acetate-hexane) to afford 4-chloro-6-methylpyrimidine (0.6 g, 3.08 mmol, 46% yield) as a colorless gummy liquid. LCMS (ESI) *m/e* 129.0 [$(M+H)^+$, calcd for $C_5H_6ClN_2$ 129.0]; LC/MS retention time (method D): t_R = 1.36 min.



Part B. (S)-tert-butyl (1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-6-methylpyrimidine (0.05 g, 0.233 mmol), (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.110 g, 0.233 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.019 g, 0.023 mmol) and Cs_2CO_3 (0.228 g, 0.700 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.03 g, 0.038 mmol, 16% yield) as a yellowish semi-solid which was carried forward without further purification. LCMS (ESI) *m/e* 436.2 [$(M+H)^+$, calcd for $C_{23}H_{32}F_2N_3O_3$ 436.2]; LC/MS retention time (Method A1): t_R = 2.91 min.

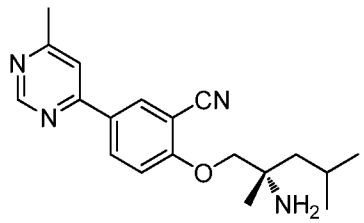


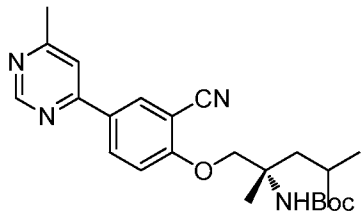
Part C. (S)-1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.03 g, 0.069 mmol) in MeOH (2 mL) 0° C was added 4N HCl in 1,4-dioxane (0.172 mL, 0.689 mmol) and the mixture stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (0.007 g, 0.021 mmol, 30% yield) as a yellow solid. LCMS (ESI) *m/e* 336.2 [$(M+H)^+$, calcd for $C_{18}H_{24}F_2N_3O$, 336.2]; LC/MS retention time (Method E): t_R = 1.69 min; LCMS retention time (method F): t_R = 2.09 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.08 (d, *J*=1.51 Hz, 1H) 8.02 (dd, *J*=12.30, 7.28 Hz, 1H), 7.85 (s, 1H), 7.19 (dd, *J*=12.80, 6.78 Hz, 1H), 4.04 - 4.19 (m, 2H), 2.61 (s, 3H), 1.86 (d, *J*=6.53 Hz, 1H), 1.73 (d, *J*=5.52 Hz, 1H), 1.63 (dd, *J*=14.06, 5.52 Hz, 1H), 1.41 (s, 3H), 1.04 (m, 6H) ppm.

Example 436

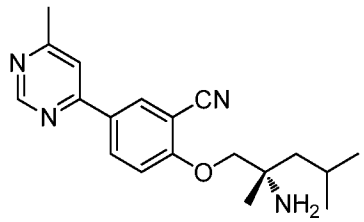
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methylpyrimidin-4-yl)benzonitrile





Part A. (S)-tert-butyl (1-(2-cyano-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-6-methylpyrimidine (0.05 g, 0.233 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 (0.107 g, 0.233 mmol) (prepared as in Example 86, Parts A and B), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.019 g, 0.023 mmol) and Cs_2CO_3 (0.228 g, 0.700 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.12 g, 0.136 mmol, 58% yield) as a yellowish semi-solid. LCMS (ESI) *m/e* 425.2 $[(M+H)^+$, calcd for $C_{24}H_{33}N_4O_3$ 425.2]; LC/MS retention time (method A1): t_R = 2.23 min.



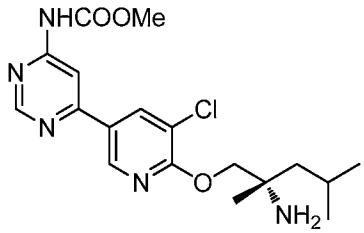
Part B. (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methylpyrimidin-4-yl)benzonitrile

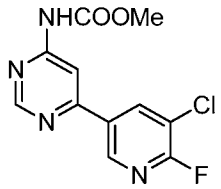
To a stirred solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.12 g, 0.136 mmol) in MeOH (2 mL) at 0 °C was added 4N HCl in 1,4-dioxane (0.339 mL, 1.357 mmol) and the mixture stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer separated, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-2-((2-

amino-2,4-dimethylpentyl)oxy)-5-(6-methylpyrimidin-4-yl)benzonitrile (0.015 g, 0.045 mmol, 33% yield) as a yellow solid. LCMS (ESI) *m/e* 325.2 [$(M+H)^+$, calcd for $C_{19}H_{25}N_4O$ 325.2]; LC/MS retention time (Method E): t_R = 1.60 min; LCMS retention time (method F): t_R = 1.92 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.04 (m, 1H), 8.48-8.52 (m, 2H), 7.92 (s, 1H), 7.38 (d, *J* = 9.20 Hz, 1H), 4.15 (s, 2H), 2.60 (s, 3H), 1.81-1.89 (m, 1H), 1.73-1.78 (m, 1H), 1.63-1.65 (m, 1H), 1.60 (s, 3H), 1.00-1.04 (m, 6H) ppm.

Example 437

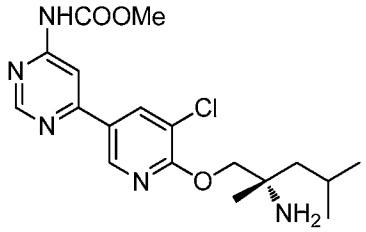
(*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-4-yl)carbamate





Part A. methyl (6-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-4-yl)carbamate

A mixture of 5-chloro-6-fluoropyridin-3-ylboronic acid (0.037 g, 0.213 mmol), methyl (6-chloropyrimidin-4-yl)carbamate (prepared as described in Example 432) (0.04 g, 0.213 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.017 g, 0.021 mmol) and Cs_2CO_3 (0.208 g, 0.640 mmol) in 1,4-dioxane (3 mL) was heated at 80 °C for 3 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford methyl (6-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-4-yl)carbamate (0.03 g, 0.035 mmol, 17% yield) as an off-white solid. LCMS (ESI) *m/e* 281.0 [$(M-H)^-$, calcd for $C_{11}H_7ClFN_4O_2$ 281.0]; LC/MS retention time (method D): t_R = 2.11 min.

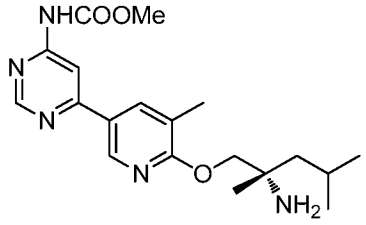


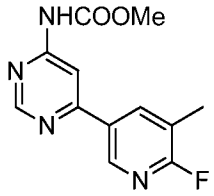
Part B. (S)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-4-yl)carbamate

A mixture of methyl (6-(5-chloro-6-fluoropyridin-3-yl)pyrimidin-4-yl)carbamate (0.03 g, 0.035 mmol), (*S*)-2-amino-2,4-dimethylpentan-1-ol (4.63 mg, 0.035 mmol) and NaH (1.411 mg, 0.035 mmol) in DMF (5 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% ethyl acetate in pet ether) to afford (*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-4-yl)carbamate (0.005 g, 0.013 mmol, 36% yield) as a yellow solid. LCMS (ESI) *m/e* 394.2 [$(M+H)^+$, calcd for $C_{18}H_{25}ClN_5O_3$ 394.2]; LC/MS retention time (Method E): t_R = 1.74 min; LCMS retention time (method F): t_R = 2.09 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.83 (t, *J*=1.51 Hz, 2H) 8.54 (d, *J*=2.01 Hz, 1H), 8.40 (d, *J*=1.51 Hz, 1H), 4.61 (d, *J*=4.52 Hz, 2H), 3.85 (s, 3H), 1.90 (d, *J*=9.54 Hz, 2H), 1.72 (s, 1H), 1.54 (s, 3H), 1.07 (m, 6H) ppm.

Example 438

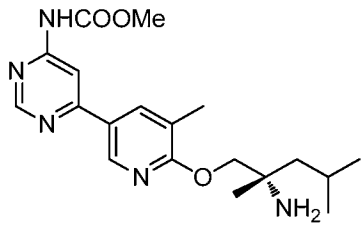
(*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate





Part A. methyl (6-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate

A mixture of 2-fluoro-3-methylpyridine-5-boronic acid (0.033 g, 0.213 mmol), methyl (6-chloropyrimidin-4-yl)carbamate (prepared as described in Example 432) (0.04 g, 0.213 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.017 g, 0.021 mmol) and Cs_2CO_3 (0.208 g, 0.640 mmol) in 1,4-dioxane (3 mL) was heated at 80 °C for 3 h. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate and the filtrate was concentrated under reduced pressure to afford methyl (6-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate (0.03 g, 0.059 mmol, 28% yield) as an off-white solid which was carried forward without further purification. LCMS (ESI) *m/e* 263.2 [$(M+H)^+$, calcd for $C_{12}H_{12}FN_4O_2$ 263.1]; LC/MS retention time (method H): t_R = 2.00 min.



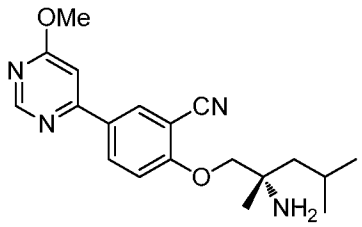
Part B. (S)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate

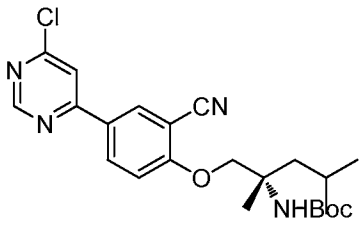
A mixture of methyl (6-(6-fluoro-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate (0.03 g, 0.063 mmol), (*S*)-2-amino-2,4-dimethylpentan-1-ol (8.26 mg, 0.063 mmol) and NaH (2.52 mg, 0.063 mmol) in DMF (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% ethyl acetate in pet ether) to afford (*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate (0.008 g, 0.020 mmol, 31% yield) as a yellow solid. LCMS (ESI) *m/e* 374.2

[$(M+H)^+$, calcd for $C_{19}H_{28}N_5O_3$ 374.2]; LC/MS retention time (Method E): t_R = 1.71 min; LCMS retention time (method F): t_R = 1.91 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.76 - 8.81 (m, 1H), 8.69 (d, *J*=3.01 Hz, 1H), 8.32 - 8.39 (m, 1H), 8.17 - 8.23 (m, 1H), 4.27 (s, 2H), 3.85 (s, 3H), 2.36 (s, 3H), 1.81 - 1.92 (m, 1H), 1.58 (dd, *J*=14.06, 5.52 Hz, 2H), 1.29 (s, 3H), 1.02 (m, 6H) ppm.

Example 439

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methoxypyrimidin-4-yl)benzonitrile

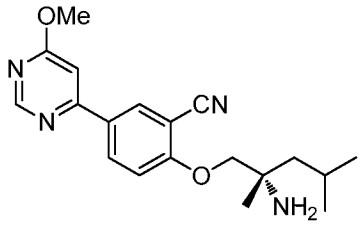




Part A. (S)-tert-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4,6-dichloropyrimidine (0.05 g, 0.336 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 (prepared as in Example 86, Parts A and B) (0.154 g, 0.336 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.027 g, 0.034 mmol) and Cs_2CO_3 (0.328 g, 1.007 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% ethyl acetate in pet ether) to afford (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.15 g, 0.246 mmol, 73% yield) as a yellowish semi-solid. LCMS (ESI) *m/e* 389.2 [(M+H-

^{t}Bu)$^+$, calcd for $C_{23}H_{30}ClN_4O_3$ 445.2]; LC/MS retention time (Method A1): t_R = 2.89 min.

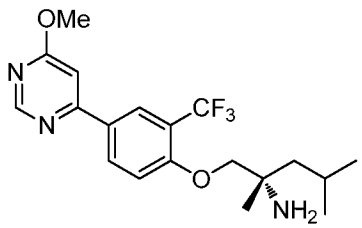


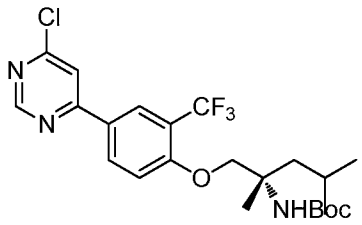
Part B. (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methoxypyrimidin-4-yl)benzonitrile

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.112 mmol) in MeOH (2 mL) at 0 °C was added 4N HCl in 1,4-dioxane (0.281 mL, 1.124 mmol). The mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by prep HPLC (method A) to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methoxypyrimidin-4-yl)benzonitrile (0.006 g, 0.018 mmol, 16% yield) as a yellow solid. LCMS (ESI) *m/e* 341.2 [(M+H)$^+$, calcd for $C_{19}H_{25}N_4O_2$ 341.2]; LCMS retention time (method F): t_R = 2.16 min. ^{1}H NMR (300 MHz, *METHANOL-d4*): δ 8.79 (d, *J*=0.76 Hz, 1H), 8.36 - 8.45 (m, 2H), 7.30 - 7.37 (m, 2H), 4.05 (s, 5H), 1.77 - 1.93 (m, 1H), 1.62 (dd, *J*=11.90, 5.48 Hz, 2H), 1.32 (s, 3H), 1.02 (m, 6H) ppm.

Example 440

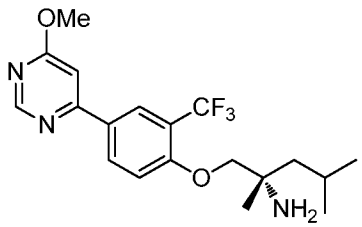
(*S*)-1-(4-(6-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine





Part A. (S)-tert-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4,6-dichloropyrimidine (0.1 g, 0.671 mmol), (*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 215) (0.337 g, 0.671 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.055 g, 0.067 mmol) and Cs_2CO_3 (0.656 g, 2.014 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.25 g, 0.458 mmol, 68% yield) as a yellowish semi-solid. LCMS (ESI) *m/e* 432.2 [(M+H-^{t}Bu)$^+$, calcd for $C_{23}H_{30}ClF_3N_3O_3$ 488.2]; LC/MS retention time (Method A1): t_R = 3.15 min.



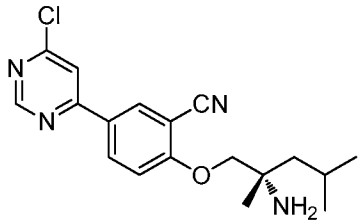
Part B. (S)-1-(4-(6-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.05 g, 0.102 mmol) in MeOH (2 mL) at 0 °C was added 4N HCl in 1,4-dioxane (0.256 mL, 1.025 mmol) and the mixture warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was

purified by prep HPLC (Method A) to afford (*S*)-1-(4-(6-methoxypyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (0.006 g, 0.015 mmol, 15% yield) as a yellow solid. LCMS (ESI) *m/e* 384.2 [$(M+H)^+$, calcd for $C_{19}H_{25}F_3N_3O_2$ 384.2]; LCMS retention time (method F): t_R = 2.66 min. ^{1}H NMR (300 MHz, *METHANOL-d4*): δ 8.79 (d, *J*=0.76 Hz, 1H), 8.41 (d, *J*=1.89 Hz, 1H), 8.30 - 8.37 (m, 1H), 7.30 - 7.37 (m, 2H), 4.00 - 4.12 (m, 5H), 1.78 - 1.91 (m, 1H), 1.61 (dd, *J*=12.65, 5.48 Hz, 2H), 1.33 (s, 3H), 1.00 (m, 6H), ppm.

Example 441

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-chloropyrimidin-4-yl)benzonitrile

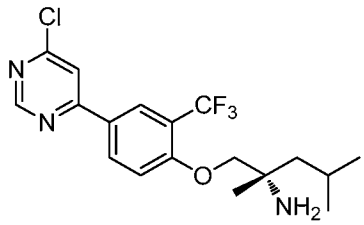


To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 439) (0.05 g, 0.112 mmol) in DCM (2 mL) at 0 °C, was added TFA (0.087 mL, 1.124 mmol) and the mixture warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by prep HPLC (Method A) to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-chloropyrimidin-4-yl)benzonitrile (0.006 g, 0.017 mmol, 15% yield) as a yellow solid. LCMS (ESI) *m/e* 345.2 [$(M+H)^+$, calcd for $C_{18}H_{22}ClN_4O$ 345.1]; LC/MS retention time (Method E): t_R = 1.82 min; LCMS retention time (method F): t_R = 2.31 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.00 (d, *J*=1.00 Hz, 1H), 8.56 (d, *J*=2.01 Hz, 1H), 8.49 - 8.53 (m, 1H), 8.13 (d, *J*=1.00 Hz, 1H), 7.37 (d, *J*=9.04 Hz, 1H), 4.06 (d, *J*=1.51 Hz, 2H), 1.86 (s, 1H), 1.54 - 1.70 (m, 2H), 1.31 (s, 3H), 1.02 (m, 6H), ppm.

Example 442

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

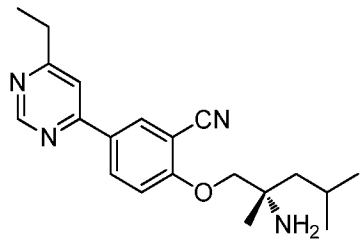
2-amine

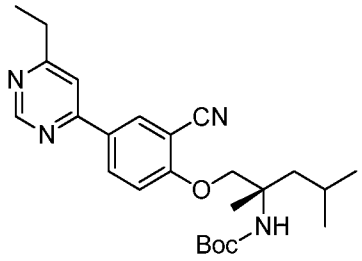


To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 440) (0.05 g, 0.102 mmol) in DCM (2 mL) at 0 °C was added TFA (0.079 mL, 1.025 mmol) and the mixture warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by prep HPLC (Method A) to afford to afford (*S*)-1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (0.03 g, 0.077 mmol, 75% yield) as a yellow solid. LCMS (ESI) *m/e* 388.2 [$(M+H)^+$, calcd for $C_{18}H_{22}ClF_3N_3O$ 388.1]; LC/MS retention time (Method E): t_R = 2.08 min; LCMS retention time (method F): t_R = 2.83 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 9.00 (d, *J*=1.00 Hz, 1H), 8.53 (d, *J*=2.01 Hz, 1H), 8.45 (dd, *J*=8.78, 2.26 Hz, 1H), 8.14 (d, *J*=1.00 Hz, 1H), 7.36 (d, *J*=9.04 Hz, 1H), 3.97 - 4.06 (m, 2H), 1.84 (s, 1H), 1.57 (dd, *J*=10.54, 5.52 Hz, 2H), 1.28 (s, 3H), 0.96 - 1.04 (m, 6H) ppm.

Example 443

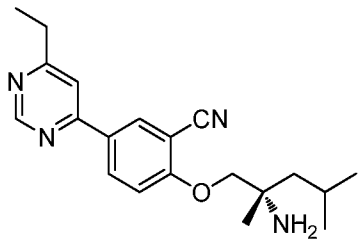
(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-ethylpyrimidin-4-yl)benzonitrile





Part A. (S)-tert-butyl (1-(2-cyano-4-(6-ethylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-cyanophenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 439) (0.1 g, 0.225 mmol), ethylboronic acid (0.025 g, 0.337 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (9.18 mg, 0.011 mmol) and Cs_2CO_3 (0.220 g, 0.674 mmol) in 1,4-dioxane (5 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (20 % ethyl acetate in hexane) to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(6-ethylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.11 g, 0.029 mmol, 13% yield) as a yellowish semi-solid. LCMS (ESI) *m/e* 439.2 $[(M+H)^+$, calcd for $C_{25}H_{35}N_4O_3$ 439.2]; LC/MS retention time (Method A1): t_R = 2.37 min.



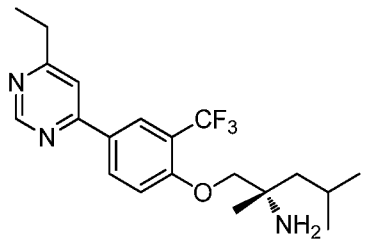
Part B. (S)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-ethylpyrimidin-4-yl)benzonitrile

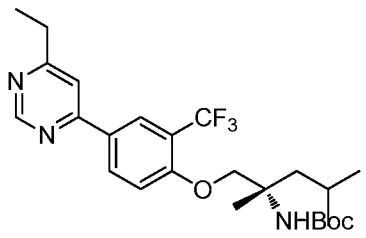
To a stirred solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(6-ethylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.1 g, 0.228 mmol) in DCM (2 mL) at 0 °C was added TFA (0.176 mL, 2.280 mmol) and the mixture warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The

organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative LC/MS (Method A) to afford (*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-ethylpyrimidin-4-yl)benzonitrile (0.005 g, 0.014 mmol, 6% yield) as a yellow solid. LCMS (ESI) *m/e* 339.2 [$(M+H)^+$, calcd for $C_{20}H_{27}N_4O$ 339.2]; LC/MS retention time (Method E): t_R = 1.77 min. ^1H NMR (400 MHz, *CD_3OD*): δ 9.06-9.07 (m, 1H), 8.49-8.55 (m, 2H), 7.91 (d, *J* = 1.60 Hz, 1H), 7.39 (d, *J* = 8.80 Hz, 1H), 4.19-4.29 (m, 2H), 2.87 (q, *J* = 23.20 Hz, 2H), 1.00-1.04 (m, 6H), 1.38-1.43 (m, 6H), 1.62-1.67 (m, 1H), 1.77-1.88 (m, 2H), ppm.

Example 444

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

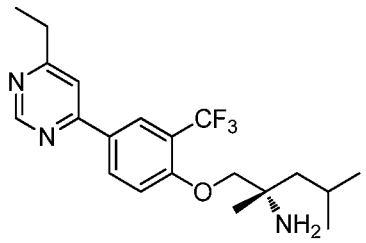




Part A. (S)-tert-butyl (1-(4-(6-ethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of (*S*)-*tert*-butyl (1-(4-(6-chloropyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 440) (0.1 g, 0.232 mmol), ethylboronic acid (0.026 g, 0.347 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (9.46 mg, 0.012 mmol) and Cs_2CO_3 (0.226 g, 0.695 mmol) in 1,4-dioxane (5 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under

reduced pressure and the residue was purified by silica gel chromatography (20 % ethyl acetate in hexane) to afford (*S*)-*tert*-butyl (1-(4-(6-ethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.12 g, 0.075 mmol, 32% yield) as yellow semi-solid. LCMS (ESI) *m/e* 482.2 [$(M+H)^+$, calcd for $C_{25}H_{35}F_3N_3O_3$ 482.2]; LC/MS retention time (Method A1): t_R = 2.78 min.

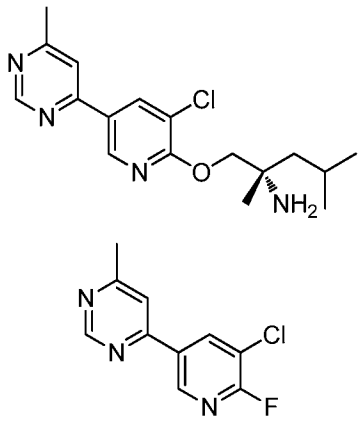


Part B. (*S*)-1-(4-(6-ethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

To a stirred solution of (*S*)-*tert*-butyl (1-(4-(6-ethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.1 g, 0.208 mmol) in DCM (2 mL) at 0 °C was added TFA (0.160 mL, 2.077 mmol) and the mixture warmed to room temperature and stirred for 2 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by preparative LC/MS (Method A) to afford (*S*)-1-(4-(6-ethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine (0.005 g, 0.013 mmol, 6% yield) as a yellow solid. LCMS (ESI) *m/e* 382.2 [$(M+H)^+$, calcd for $C_{20}H_{27}F_3N_3O$ 382.2]; LC/MS retention time (Method E): t_R = 2.22 min; LCMS retention time (method F): t_R = 2.78 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 9.06 (d, *J* = 1.20 Hz, 1H), 8.43-8.50 (m, 2H), 7.91 (d, *J* = 1.20 Hz, 1H), 7.39 (d, *J* = 8.80 Hz, 1H), 4.13-4.18 (m, 2H), 2.85-2.91 (m, 2H), 1.82-1.87 (m, 1H), 1.74-1.79 (m, 1H), 1.62-1.67 (m, 1H), 1.29-1.43 (m, 6H), 0.98-1.05 (m, 6H) ppm.

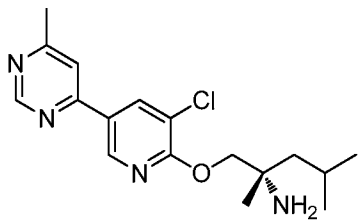
Example 445

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



Part A. 4-(5-chloro-6-fluoropyridin-3-yl)-6-methylpyrimidine

A mixture of (5-chloro-6-fluoropyridin-3-yl)boronic acid (0.055 g, 0.311 mmol), 4-chloro-6-methylpyrimidine (0.04 g, 0.311 mmol), $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.025 g, 0.031 mmol) and Cs_2CO_3 (0.304 g, 0.933 mmol) in 1,4-dioxane (3 mL) was heated at 80 °C for 3 h. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford 4-(5-chloro-6-fluoropyridin-3-yl)-6-methylpyrimidine (0.035 g, 0.090 mmol, 29% yield) as a brown solid. LCMS (ESI) *m/e* 224.5 $[(M+H)^+$, calcd for $C_{10}H_8ClFN_3$ 224.0]; LC/MS retention time (method B): t_R = 0.86 min.



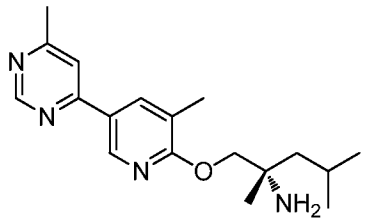
Part B. (S)-1-((3-chloro-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

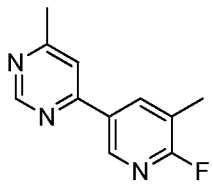
A mixture of 4-(5-chloro-6-fluoropyridin-3-yl)-6-methylpyrimidine (0.035 g, 0.157 mmol) (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.021 g, 0.157 mmol) and KO^{t}Bu (0.470 mL 0.470 mmol) in tetrahydrofuran (5 mL) was stirred at RT overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford (*S*)-1-((3-chloro-5-(6-

methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.008 g, 0.024 mmol, 15% yield) as a yellow solid. LCMS (ESI) *m/e* 335.2 [(M+H)$^+$, calcd for $C_{17}H_{24}ClN_4O$ 335.2]; LC/MS retention time (Method E): t_R = 1.88 min; LCMS retention time (method F): t_R = 2.32 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 9.07 (d, *J* = 1.20 Hz, 1H), 8.93 (d, *J* = 2.00 Hz, 1H), 8.64 (d, *J* = 2.40 Hz, 1H), 7.95 (d, *J* = 0.40 Hz, 1H), 4.60-4.64 (m, 2H), 2.62 (s, 3H), 1.88-1.93 (m, 2H), 1.69-1.75 (m, 1H), 1.54 (s, 3H), 1.08-1.07 (m, 6H) ppm.

Example 446

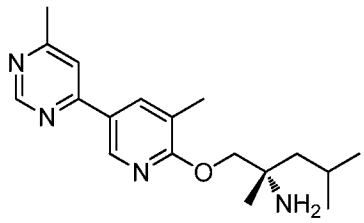
(*S*)-2,4-dimethyl-1-((3-methyl-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine





Part A. 4-(6-fluoro-5-methylpyridin-3-yl)-6-methylpyrimidine

To a solution of 2-fluoro-3-methylpyridine-5-boronic acid (0.048 g, 0.311 mmol) in 1,4-dioxane (3 mL), 4-chloro-6-methylpyrimidine (0.04 g, 0.311 mmol) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.025 g, 0.031 mmol) and Cs_2CO_3 (0.304 g, 0.933 mmol). The reaction mixture was heated at 80 °C for 3 h. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to afford 4-(6-fluoro-5-methylpyridin-3-yl)-6-methylpyrimidine (0.04 g, 0.160 mmol, 52% yield) as a brown solid. LCMS (ESI) *m/e* 204.2 [(M+H)$^+$, calcd for $C_{11}H_{11}FN_3$ 204.1]; LC/MS retention time (Method A1): t_R = 2.30 min.

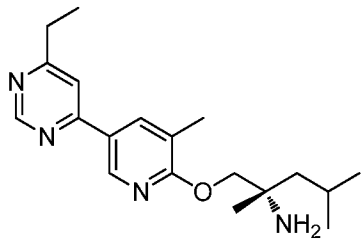


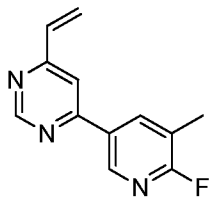
Part B. (S)-2,4-dimethyl-1-((3-methyl-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine

A mixture of 4-(6-fluoro-5-methylpyridin-3-yl)-6-methylpyrimidine (0.04 g, 0.197 mmol) KO^{t}Bu (0.591 mL, 0.591 mmol) and (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.026 g, 0.197 mmol) in tetrahydrofuran (5 mL) was stirred at RT overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure and purified by preparative LC/MS (Method A) to afford (*S*)-2,4-dimethyl-1-((3-methyl-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine (0.049 g, 0.152 mmol, 77% yield) as a yellow solid. LCMS (ESI) *m/e* 315.2 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$ 315.2]; LC/MS retention time (Method E): t_R = 1.81 min; LCMS retention time (method F): t_R = 1.87 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 9.03 (d, *J* = 1.20 Hz, 1H), 8.81-8.82 (m, 1H), 8.33-8.33 (m, 1H), 7.90 (d, *J* = 0.80 Hz, 1H), 4.46 (s, 2H), 2.61 (s, 3H), 2.29 (s, 3H), 1.88-1.93 (m, 1H), 1.77-1.82 (m, 1H), 1.63-1.68 (m, 1H), 1.45 (s, 3H), 1.03-1.08 (m, 6H) ppm.

Example 447

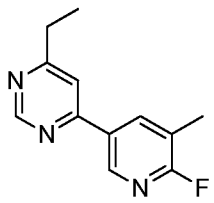
(*S*)-1-((5-(6-ethylpyrimidin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine





Part A. 4-(6-fluoro-5-methylpyridin-3-yl)-6-vinylpyrimidine

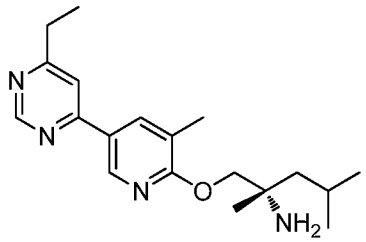
A mixture of 4-chloro-6-vinylpyrimidine (prepared from 4,6-dichloropyrimidine using procedure described in Example 315, Part B) (0.03 g, 0.213 mmol), 2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.051 g, 0.213 mmol), and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.017 g, 0.021 mmol) and Cs_2CO_3 (0.209 g, 0.640 mmol) in 1,4-dioxane (2 mL) was heated at 80 °C overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (20 % ethyl acetate in hexane) to afford 4-(6-fluoro-5-methylpyridin-3-yl)-6-vinylpyrimidine (0.05 g, 0.151 mmol, 71% yield) as a yellowish semi-solid. LCMS (ESI) *m/e* 216.2 [$(M+H)^+$, calcd for $C_{12}H_{11}FN_3$ 216.1]; LC/MS retention time (Method A1): t_R = 2.38 min.



Part B. 4-ethyl-6-(6-fluoro-5-methylpyridin-3-yl)pyrimidine

To a solution of 4-(6-fluoro-5-methylpyridin-3-yl)-6-vinylpyrimidine (0.05 g, 0.232 mmol) in tetrahydrofuran (5 mL), was added palladium on carbon (0.025 g, 0.023 mmol) and stirred at room temperature overnight under 1 atm of hydrogen gas. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to afford 4-ethyl-6-(6-fluoro-5-methylpyridin-3-yl)pyrimidine (0.04 g, 0.121 mmol, 52% yield) as a yellowish semi-

solid. LCMS (ESI) *m/e* 218.2 [(M+H)$^+$, calcd for $C_{12}H_{13}FN_3$ 218.1]; LC/MS retention time (method D): t_R = 1.83 min.

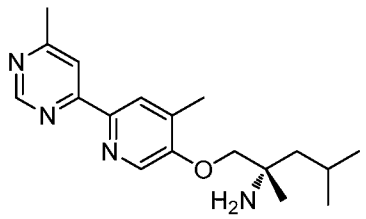


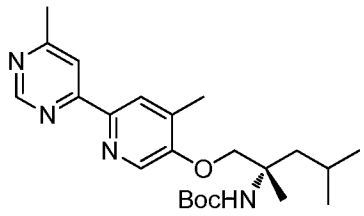
Part C. (S)-1-((5-(6-ethylpyrimidin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine

A mixture of 4-ethyl-6-(6-fluoro-5-methylpyridin-3-yl)pyrimidine (0.04 g, 0.184 mmol), (*S*)-2-amino-2,4-dimethylpentan-1-ol (0.024 g, 0.184 mmol), and KO^{t}Bu (0.552 mL, 0.552 mmol) in tetrahydrofuran (3 mL) was stirred at RT overnight. The reaction mixture was cooled to room temperature then filtered through diatomaceous earth (Celite®), washing the bed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure and purified by preparative LC/MS (Method A) to afford (*S*)-1-((5-(6-ethylpyrimidin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine (0.008 g, 0.022 mmol, 12% yield)) as a yellow solid. LCMS (ESI) *m/e* 329.3 [(M+H)$^+$, calcd for $C_{19}H_{29}N_4O$ 329.2]; LC/MS retention time (Method E): t_R = 1.11 min; LCMS retention time (method F): t_R = 1.38 min. ^{1}H NMR (400 MHz, *CD_3OD*): δ 9.05 (d, *J* = 1.20 Hz, 1H), 8.81-8.82 (m, 1H), 8.33-8.34 (m, 1H), 7.88 (d, *J* = 1.20 Hz, 1H), 4.53 (s, 2H), 2.87 (q, *J* = 22.80 Hz, 2H), 2.39 (s, 3H), 1.84-1.91 (m, 2H), 1.67-1.72 (m, 1H), 1.51 (s, 3H), 1.37 (s, 3H), 0.99-1.08 (m, 6H) ppm.

Example 450

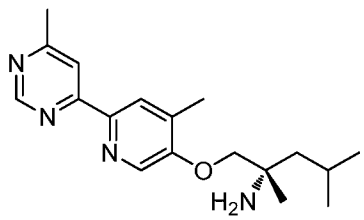
(*S*)-2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine





Part A. (S)-Tert-butyl (2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-yl)carbamate

A 4-chloro-6-methylpyrimidine (0.1 g, 0.778 mmol), (*S*)-*tert*-butyl (1-((6-chloro-4-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (prepared in a similar fashion as described in Example 226) (0.278 g, 0.778 mmol) and hexamethylditin (0.242 mL, 1.167 mmol) in 1,4-dioxane (3 mL) was flushed with nitrogen for 10 min. $Pd(Ph_3P)_4$ 4 (0.090 g, 0.078 mmol) was added and the reaction mixture was flushed with nitrogen for 5 min. The reaction mixture was heated in a microwave at 150 °C for 90 min. The reaction mixture was then filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and crude product was purified by silica gel chromatography (20 % ethyl acetate in hexane) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-yl)carbamate (0.1 g, 0.190 mmol, 25% yield). LCMS (ESI) *m/e* 415.2 $[(M+H)^+$, calcd for $C_{23}H_{35}N_4O_3$ 415.2]; LC/MS retention time (Method G): t_R = 3.83 min.



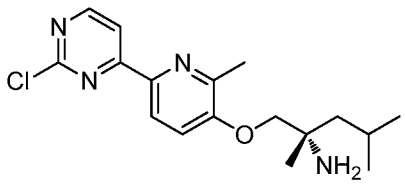
Part B. (S)-2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine

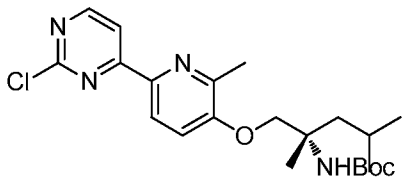
A solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-yl)carbamate (0.08 g, 0.193 mmol) in methanol (2 mL) was cooled to 0° C and 4M HCl in 1,4-dioxane (0.482 mL, 1.930 mmol) was added and the mixture stirred at room temperature for 1 h. The reaction mixture diluted with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl

acetate (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method C) to afford (*S*)-2,4-dimethyl-1-((4-methyl-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine (0.039 g, 0.120 mmol, 62% yield) as a pale yellow solid. LCMS (ESI) *m/e* 315.3 $[(M+H)^+$, calcd for $C_{18}H_{27}N_4O$ 315. 2]; LC/MS retention time (method H): t_R = 1.21 min; LC/MS retention time (method I): t_R = 0.92 min. ^{1}H NMR(400 MHz, methanol-d_4): δ 9.05 (d, *J*=1.00 Hz, 1 H), 8.39 (s, 1 H), 8.35 (s, 1 H), 8.23 (s, 1 H), 4.25 (d, *J*=10.54 Hz, 2 H), 2.62 (s, 3 H), 2.45 (s, 3 H), 1.81 - 1.91 (m, 2 H), 1.64 - 1.76 (m, 1 H), 1.49 (s, 3 H), 1.05 (m, 6 H) ppm.

Example 451

(*S*)-1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

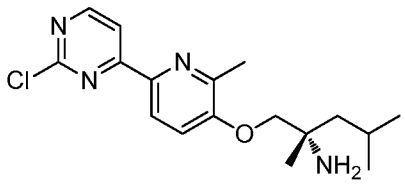




Part A. (S)-tert-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate

A solution 2,4-dichloropyrimidine (0.1 g, 0.671 mmol), (*S*)-*tert*-butyl (1-((6-iodo-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (prepared in similar fashion as described for 343) (0.301 g, 0.671 mmol) and hexamethylditin (0.139 mL, 0.671 mmol) in 1,4-dioxane (3 mL) was flushed with nitrogen for 10 min. $Pd(Ph_3P)_4$ (0.039 g, 0.034 mmol) was added and the reaction mixture was flushed with nitrogen for 5 min. The reaction mixture was heated in a microwave at 150 °C for 90 min. The reaction mixture was then filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and crude product was purified by silica gel

chromatography (20 % ethyl acetate in hexane) to afford (*S*)-*tert*-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.02 g, 0.043 mmol, 7% yield). LCMS (ESI) *m/e* 435.2 $[(M+H)^+$, calcd for $C_{22}H_{32}ClN_4O_3$ 435.2]; LC/MS retention time (Method G): t_R = 4.07 min.

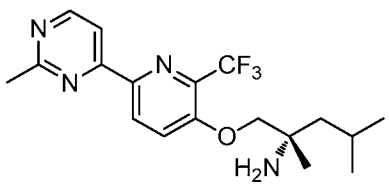


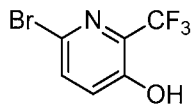
Part B. (S)-1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine

A solution of (*S*)-*tert*-butyl (1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-yl)carbamate (0.02 g, 0.046 mmol) in DCM (5 mL) was cooled to 0° C and TFA (3.54 µl, 0.046 mmol) was added. The reaction mixture was stirred at room temperature for 4 h then the mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine (0.008 g, 0.022 mmol, 49% yield) as a pale yellow solid. LCMS (ESI) *m/e* 335.3 $[(M+H)^+$, calcd for $C_{17}H_{24}ClN_4O$, 335.2]; LC/MS retention time (method H): t_R = 1.53 min; LC/MS retention time (method I): t_R = 1.19 min. ^{1}H NMR (400 MHz, methanol-d_4): δ 8.71 - 8.77 (m, 1 H), 8.31 - 8.40 (m, 2 H), 7.49 - 7.60 (m, 1 H), 4.14 - 4.30 (m, 2 H), 2.64 (br. s., 3 H), 1.82 - 1.97 (m, 2 H), 1.69 - 1.81 (m, 1 H), 1.55 (s, 3 H), 1.00 - 1.15 (m, 6 H) ppm.

Example 454

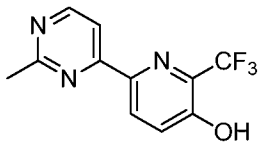
(*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine





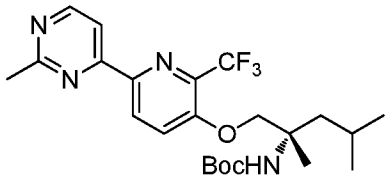
Part A. 6-bromo-2-(trifluoromethyl)pyridin-3-ol

To a solution of 2-(trifluoromethyl)pyridin-3-ol (1.0 g, 6.13 mmol) in DMF (5 mL) at 0 °C was added NBS (1.091 g, 6.13 mmol) and the mixture was warmed to room temperature and stirred overnight. After reaction mixture diluted with water (50 mL) and extracted with dichloromethane (80 mL). The organic layer was washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (12% ethyl acetate in pet ether) to afford 6-bromo-2-(trifluoromethyl)pyridin-3-ol (0.5 g, 1.984 mmol, 32% yield). LCMS (ESI) *m/e* 241.8 [$(M+H)^+$, calcd for $C_6H_4BrF_3NO$, 241.9]; LC/MS retention time (method NA): t_R = 1.99 min.



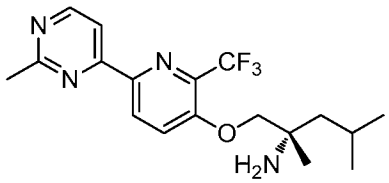
Part B. 6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-ol

A solution of 4-chloro-2-methylpyrimidine (0.1 g, 0.778 mmol), 6-bromo-2-(trifluoromethyl)pyridin-3-ol (0.207 g, 0.856 mmol), and hexamethylditin (0.242 mL, 1.167 mmol) in 1,4-dioxane (3 mL) was flushed with nitrogen. $Pd(Ph_3P)_4$ (0.045 g, 0.039 mmol) was added and the mixture was flushed for a further 5 min with nitrogen. The reaction mixture was heated in a microwave at 150 °C for 90 min. The reaction mixture was then filtered through a diatomaceous earth (Celite®) bed, washing with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and crude product was purified by silica gel chromatography (20% ethyl acetate in pet ether) to afford 6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-ol (0.06 g, 0.207 mmol, 27% yield). LCMS (ESI) *m/e* 256.0 [$(M+H)^+$, calcd for $C_{11}H_9F_3N_3O$ 256.1]; LC/MS retention time (method B): t_R = 2.50 min.



Part C. (*S*)-*tert*-butyl (2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-yl)carbamate

To a solution of 6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-ol (0.09 g, 0.166 mmol) in DMF (3 mL) was added NaH (0.020 g, 0.497 mmol) and (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (0.049 g, 0.166 mmol). The brown colored solution was stirred at 80 °C overnight. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (20 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (15% ethyl acetate in pet ether) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-yl)carbamate (0.1 g, 0.092 mmol, 55% yield). LCMS (ESI) *m/e* 469.2 [$(M+H)^+$, calcd for $C_{23}H_{32}F_3N_4O_3$, 469.2]; LC/MS retention time (Method G): t_R = 1.35 min.



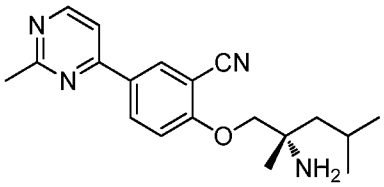
Part D. (S)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine

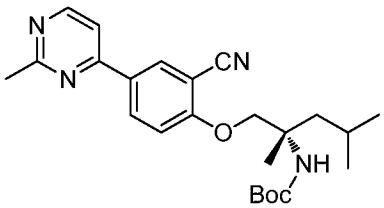
To a solution of (*S*)-*tert*-butyl (2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-yl)carbamate (0.1 g, 0.092 mmol) in DCM (5 mL) cooled to 0° C was added TFA (7.07 µl, 0.092 mmol) and the reaction mixture stirred at room temperature for 1 h. The reaction mixture diluted with saturated sodium bicarbonate (20 mL) and extracted with ethyl acetate(30 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-

yl)oxy)pentan-2-amine (0.005 g, 0.013 mmol, 14% yield) as a pale yellow solid. LCMS (ESI) *m/e* 369.3 [$(M+H)^+$, calcd for $C_{18}H_{24}F_3N_4O$ 369.2]; LC/MS retention time (method H): t_R = 1.76 min; LC/MS retention time (method I): t_R = 1.16 min. ^1H NMR(400 MHz, methanol-d_4): δ 8.75 - 8.82 (m, 2 H), 8.20 (d, *J*=5.02 Hz, 1 H), 7.88 (d, *J*=9.04 Hz, 1 H), 4.12 (d, *J*=4.02 Hz, 2 H), 2.78 (s, 3 H), 1.86 (s, 1 H), 1.63 (dd, *J*=16.06, 5.52 Hz, 2 H), 1.35 (s, 3 H), 1.02 (m, 6 H) ppm.

Example 458

(*S*)-2-(2-amino-2, 4-dimethylpentyloxy)-5-(2-methylpyrimidin-4-yl) benzonitrile

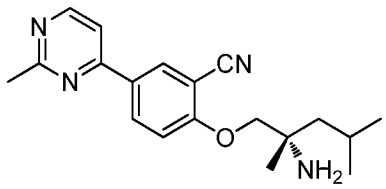




Part A: (S)-tert-butyl (1-(2-cyano-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A solution of 4-chloro-2-methylpyrimidine (0.05 g, 0.389 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 (prepared as in Example 86, Parts A and B) (0.178 g, 0.389 mmol), potassium phosphate, tribasic (0.083 g, 0.389 mmol), and KBr (0.046 g, 0.389 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen gas for 10 min. $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.032 g, 0.039 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated under reduced pressure then dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-

(2-cyano-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.07 g, 0.122 mmol, 31% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 425.2 [$(M+H)^+$, calcd for $C_{24}H_{32}N_4O_3$ 425.2]; LC/MS retention time (Method A1): t_R = 2.54 min.

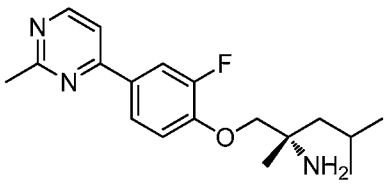


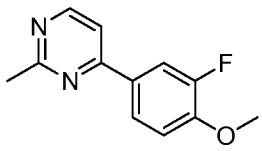
Part B: (S)-2-(2-amino-2,4-dimethylpentyloxy)-5-(2-methylpyrimidin-4-yl)benzonitrile

To a solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (70 mg, 0.122 mmol) in DCM (2 mL) at 0 °C was added TFA (0.188 mL, 2.440 mmol) and the mixture stirred for 5 min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method C) to afford (*S*)-2-(2-amino-2, 4-dimethylpentyloxy)-5-(2-methylpyrimidin-4-yl) benzonitrile (48 mg, 0.108 mmol, 89% yield) as a pale yellow solid. LCMS (ESI) *m/e* 325.0 [$(M+H)^+$, calcd for $C_{19}H_{25}N_4O$ 325.2]; LC/MS retention time (method H): t_R = 1.27 min; LC/MS retention time (method I): t_R = 0.92 min. ^{1}H NMR(400 MHz, Methanol-d4): δ 8.73 (d, *J* = 5.60 Hz, 1H), 8.53-8.60 (m, 2H), 7.85 (d, *J* = 5.60 Hz, 1H), 7.45 (d, *J* = 9.20 Hz, 1H), 4.32-4.38 (m, 2H), 2.78 (s, 3H), 1.89-2.00 (m, 2H), 1.72-1.77 (m, 1H), 1.57 (s, 3H), 1.06-1.11 (m, 6H) ppm.

Example 462

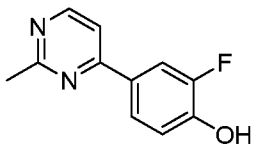
(*S*)-1-(2-fluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





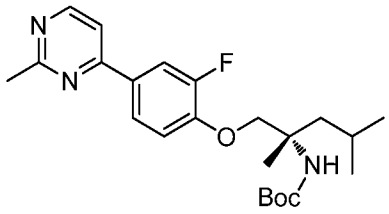
Part A: 4-(3-fluoro-4-methoxyphenyl)-2-methylpyrimidine

A mixture of 4-chloro-2-methylpyrimidine (0.2 g, 1.556 mmol), (3-fluoro-4-methoxyphenyl)boronic acid (0.264 g, 1.556 mmol), and Cs_2CO_3 (1.014 g, 3.11 mmol) in 1,4-dioxane (5 mL) and water (3 mL) was purged with nitrogen gas for 30 min. The reaction mixture was added $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.127 g, 0.156 mmol) and was again purged with nitrogen gas for 10 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was taken up in ethyl acetate (50 mL) and water (40 mL), then the biphasic mixture was filtered through celite. The celite was washed with ethyl acetate (50 mL). The aqueous layer was separated out and the organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to afford a brown solid. The crude solid was purified by silica gel chromatography (EtOAc in pet ether) to afford 4-(3-fluoro-4-methoxyphenyl)-2-methylpyrimidine (0.128 g, 0.587 mmol, 38% yield) as a light yellow solid as an off-white color solid. LCMS (ESI) *m/e* 219.1 $[(M+H)^+$, calcd for $C_{12}H_{12}FN_2O$ 219.1]; LC/MS retention time (method B): t_R = 0.69 min.



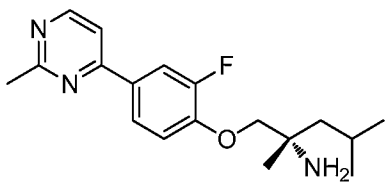
Part B: 2-fluoro-4-(2-methylpyrimidin-4-yl) phenol

To 4-(3-fluoro-4-methoxyphenyl)-2-methylpyrimidine (0.128 g, 0.587 mmol) at 0 °C was added HBr in AcOH (34%) (5 mL, 92 mmol) and the reaction mixture allowed to warm to room temperature, then heated at 100 °C for 12 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The brown residue was taken up in ethyl acetate (5 mL) and pet ether (10 mL), filtered, and dried to afford 2-fluoro-4-(2-methylpyrimidin-4-yl)phenol (0.11 g, 0.269 mmol, 46% yield) as an off-white solid which was carried forward without further purification. LCMS (ESI) *m/e* 205.2 $[(M+H)^+$, calcd for $C_{11}H_{10}FN_2O$ 205.1]; LC/MS retention time (method A1): t_R = 1.59 min.



Part C: (S)-Tert-butyl(1-(2-fluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a stirred solution of 2-fluoro-4-(2-methylpyrimidin-4-yl)phenol (0.11 g, 0.269 mmol) in DMF (5 mL) cooled to 0 °C. K_2CO_3 (0.112 g, 0.808 mmol) was added in portions to the reaction mixture followed by slow addition of (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (0.095 g, 0.323 mmol) in DMF(1 mL). The reaction mixture was slowly allowed to warm to RT and stirred at 88 °C for 12 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous .ammonium chloride solution (10 mL). The reaction mixture was extracted with ethyl acetate (2x20 mL). The combined organic layer was washed with water (2x20 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, filtered and was evaporated to dryness under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-fluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (crude yield) (0.08 g, 0.088 mmol, 33% yield) as a brown semi-solid which was carried forward without further purification. LCMS (ESI) *m/e* 418.2 $[(M+H)^+$, calcd for $C_{23}H_{33}FN_3O_3$ 418.2]; LC/MS retention time (method A1): t_R = 2.66 min.



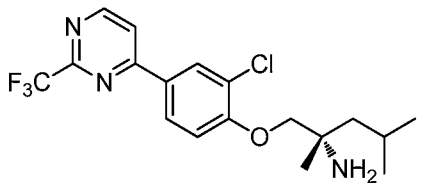
Part D: (S)-1-(3-fluoro-4-(2-methylpyrimidin-4-yl) phenoxy)-2,4-dimethylpentan-2-amine

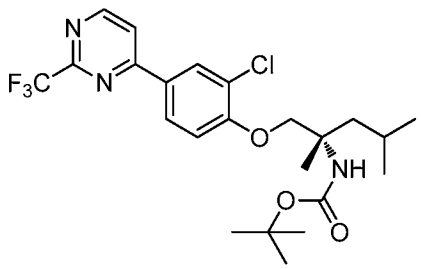
A stirred solution of (*S*)-*tert*-butyl (1-(2-fluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.08 g, 0.192 mmol) in DCM (2 mL) was cooled to 0 °C and TFA (0.295 mL, 3.83 mmol) was added and the mixture stirred for 5 min. The reaction mixture was allowed to warm to room temperature

and stirred for 4 h. The reaction mixture was evaporated under reduced pressure. The crude material was purified by preparative LC/MS (method A) to afford (*S*)-1-(3-fluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (39.9 mg, 0.129 mmol , 61% yield) as a pale yellow solid. LCMS (ESI) *m/e* 318.0 [(M+H)$^+$, calcd for C18H25FN3O 318.2]; LC/MS retention time (method H): t_R = 1.27 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.64 (d, *J* = 5.60 Hz, 1H), 7.99-8.05 (m, 2H), 7.74 (d, *J* = 5.60 Hz, 1H), 7.30 (t, *J* = 17.20 Hz, 1H), 4.08-4.17 (m, 2H), 2.73 (s, 3H), 1.74-1.87 (m, 2H), 1.61-1.64 (m, 1H), 1.42 (s, 3H), 1.00-1.05 (m, 6H) ppm.

Example 465

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

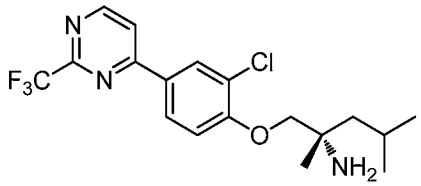




Part A: (S)-Tert-butyl(1-(2-chloro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl) carbamate

A mixture of 4-chloro-2-(trifluoromethyl)pyrimidine (0.05 g, 0.274 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 285, Part A) (0.128 g, 0.274 mmol) and Cs_2CO_3 (0.179 g, 0.548 mmol) were taken in 1,4-dioxane (6 mL) and water (1 mL). The reaction mixture was purged with nitrogen gas for 30 min and $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.022 g, 0.027 mmol) was added. The reaction mixture was again purged with nitrogen gas for another 10 min and heated at 80 °C

for 12 h. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was diluted with water (30 mL) and ethyl acetate (30 mL). The biphasic mixture was filtered through celite. The celite was washed with ethyl acetate (50 mL). The ethyl acetate layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-chloro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.07 g, 0.143 mmol, 52% yield) as a brown solid. LCMS (ESI) *m/e* 489.2 [(M+2H)$^+$, calcd for $C_{23}H_{31}ClF_3N_3O_3$ 489.2]; LC/MS retention time (Method C): t_R = 2.65 min.

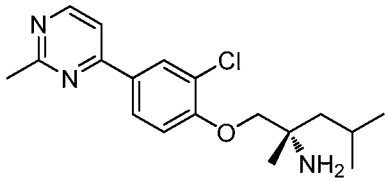


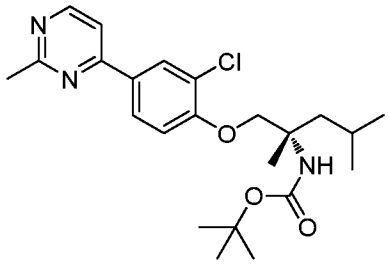
Part B: (S)-1-(2-chloro-4-(2-(trifluoromethyl) pyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-amine

To a solution of methyl (*S*)-*tert*-butyl (1-(2-chloro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.08 g, 0.164 mmol) in dichloromethane (2 mL) at 0 °C was added TFA (0.253 mL, 3.28 mmol) and the mixture stirred for 5min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford (*S*)-1-(2-chloro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (46.5 mg, 0.12 mmol, 73% yield) as a pale yellow solid . LCMS (ESI) *m/e* 388.0 [(M+H)$^+$, calcd for $C_{18}H_{22}ClF_3N_3O$ 388.1]; LC/MS retention time (method H): t_R = 1.93 min; LC/MS retention time (method I): t_R = 1.45 min. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 9.06 (d, *J* = 4.00 Hz, 1H), 8.36-8.41 (m, 2H), 8.25-8.27 (m, 1H), 7.35 (d, *J* = 8.80 Hz, 1H), 3.88-3.91 (m, 2H), 1.79-1.82 (m, 1H), 1.40-1.46 (m, 2H), 1.16 (s, 3H), 0.91-0.94 (m, 6H) ppm.

Example 469

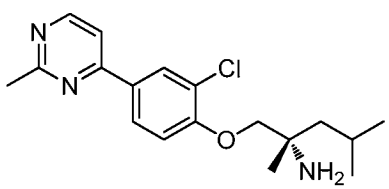
(*S*)-1-(2-chloro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





Part A: (S)-tert-butyl (1-(2-chloro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-2-methylpyrimidine (0.03 g, 0.233 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 285, Part A) (0.120 g, 0.257 mmol), Cs_2CO_3 (0.228 g, 0.700 mmol), and KBr (0.028 g, 0.233 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen gas for 30 min. $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.019 g, 0.023 mmol) was added to the reaction mixture and the solution was again purged with nitrogen gas for another 10 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated, dissolved in ethyl acetate (20 mL) and water (20 mL) and the biphasic mixture was filtered through diatomaceous earth (Celite®). The pad was washed with ethyl acetate (25 mL). The ethyl acetate layer was separated and dried over Na2SO4, filtered, and concentrated under reduced pressure which afforded crude product (*S*)-*tert*-butyl (1-(2-chloro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (crude yield) (0.06 g, 0.138 mmol, 59% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 434.2 [$(M+H)^+$, calcd for $C_{23}H_{33}ClN_3O_3$ 434.2]; LC/MS retention time (method B): t_R = 2.34 min.

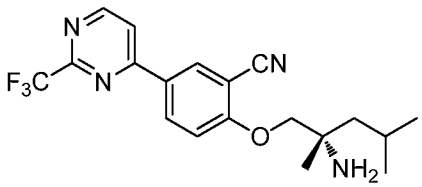


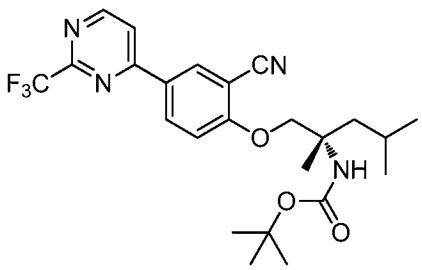
Part B: (S)-1-(2-chloro-4-(2-methylpyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-(2-chloro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.08 g, 0.184 mmol) in DCM (2 mL) at 0 °C was added TFA (0.284 mL, 3.69 mmol) and the mixture stirred for 5 min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) which afforded (*S*)-1-(2-chloro-4-(2-methylpyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-amine (22.5, 0.067 mmol, 37% yield) as a pale yellow solid. LCMS (ESI) *m/e* 334.0 [$(M+H)^+$, calcd for $C_{18}H_{25}ClN_3O$ 334.2]; LC/MS retention time (method H): t_R = 1.48 min; LC/MS retention time (method I): t_R = 1.10 min. ^{1}H NMR (400 MHz, Methanol-d4) : δ 8.68 (d, *J* = 5.60 Hz, 1H), 8.32 (d, *J* = 2.00 Hz, 1H), 8.15-8.18 (m, 1H), 7.77-7.79 (m, 1H), 7.32 (d, *J* = 8.80 Hz, 1H), 4.20-4.27 (m, 2H), 2.76 (s, 3H), 1.88-1.97 (m, 2H), 1.70-1.75 (m, 1H), 1.54 (s, 3H), 1.03-1.09 (m, 6H) ppm.

Example 474

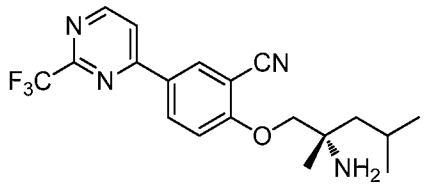
(*S*)-2-(2-amino-2,4-dimethylpentyloxy)-5-(2-(trifluoromethyl)pyrimidin-4-yl)benzonitrile





Part A: (S)-Tert-butyl (1-(2-cyano-4-(2-(trifluoromethyl) pyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-yl) carbamate

A mixture of 4-chloro-2-(trifluoromethyl)pyrimidine (0.025 g, 0.137 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 (prepared as in Example 86, Parts A and B) (0.063 g, 0.137 mmol), and Cs_2CO_3 (0.089 g, 0.274 mmol) in 1,4-dioxane (6 mL) and water (1 mL) was purged with nitrogen gas for 30 min. $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.011 g, 0.014 mmol) was added. The reaction mixture was again purged with nitrogen gas for 10 min and heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was diluted with water (30 mL) and ethyl acetate (30 mL). The biphasic mixture was filtered through celite. The celite was washed with ethyl acetate (50 mL). The ethyl acetate layer was separated, dried over Na2SO4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-cyano-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.042 g, 0.088 mmol, 64% yield) as a brown solid which was carried forward without further purification. LCMS (ESI) *m/e* 479.3 $[(M+H)^+$, calcd for $C_{24}H_{30}F_3N_4O_3$ 479.2]; LC/MS retention time (method B): t_R = 1.19 min.



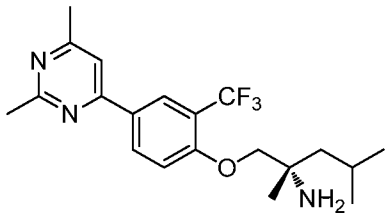
Part B: (S)-2-(2-amino-2,4-dimethylpentyloxy)-5-(2-(trifluoromethyl)pyrimidin-4-yl)benzonitrile

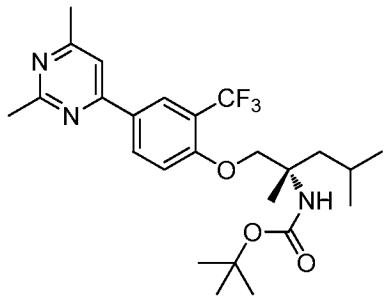
To a solution of (*S*)-*tert*-butyl (1-(2-cyano-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.035 g, 0.073 mmol) in dichloromethane (2 mL) at 0 °C was added TFA (0.113 mL, 1.463 mmol) and the mixture stirred for 5 min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method C) to afford (*S*)-2-(2-amino-2,4-dimethylpentyloxy)-5-(2-(trifluoromethyl)pyrimidin-4-yl)benzonitrile (9 mg, 0.023 mmol, 32% yield) as a pale yellow solid. LCMS (ESI) *m/e* 379.0 $[(M+H)^+$, calcd for $C_{19}H_{22}F_3N_4O$ 379.2]; LC/MS retention time (method H): t_R = 1.74 min; LC/MS retention time (method I): t_R = 1.33 min. ^{1}H NMR(400 MHz, Methanol-d4): δ 8.98

(d, J = 5.20 Hz, 1H), 8.58-8.61 (m, 2H), 8.20 (d, J = 5.60 Hz, 1H), 7.43 (d, J = 8.80 Hz, 1H), 4.18-4.23 (m, 2H), 1.77-1.90 (m, 2H), 1.62-1.67 (m, 1H), 1.42 (s, 3H), 1.04-1.06 (m, 6H) ppm.

Example 479

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

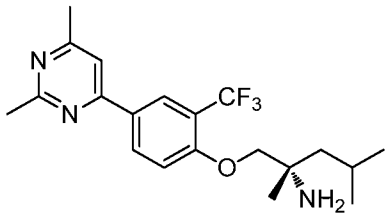




Part A: (S)-tert-butyl (1-(4-(2,6-dimethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A solution of 4-chloro-2,6-dimethylpyrimidine (0.03 g, 0.210 mmol), (*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 215, Parts A and B) (0.116 g, 0.231 mmol), Cs_2CO_3 (0.206 g, 0.631 mmol), and KBr (0.025 g, 0.210 mmol) in 1,4-dioxane (10 mL) was purged with nitrogen gas for 30 min. $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.017 g, 0.021 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated in a microwave at 80 °C for 12 h. The reaction mixture was concentrated, dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(4-(2,6-

dimethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.04 g, 0.083 mmol, 40% yield) as a brown semi-solid which was carried forward without further purification. LCMS (ESI) *m/e* 482.2 [$(M+H)^+$, calcd for $C_{25}H_{35}F_3N_3O_3$ 482.2]; LC/MS retention time (Method A1): t_R = 2.97 min.

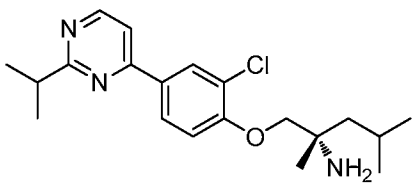


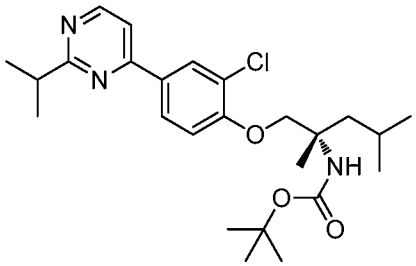
Part B: (S)-1-(4-(2,6-dimethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-(4-(2,6-dimethylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (40 mg, 0.083 mmol) in DCM (2 mL) at 0 °C was added TFA (0.128 mL, 1.661 mmol) and the mixture stirred for 5 min at 0 °C. The reaction mixture was allowed to stir for 4 h at room temperature, then was concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method B) to afford (*S*)-1-(4-(2, 6-dimethylpyrimidin-4-yl)-2-(trifluoromethyl) phenoxy)-2, 4-dimethylpentan-2-amine (43 mg, 0.075 mmol, 91% yield) as a pale yellow solid. LCMS (ESI) *m/e* 382.3 [$(M+H)^+$, calcd for $C_{20}H_{27}F_3N_3O$ 382.2]; LC/MS retention time (method H): t_R = 1.82 min; LC/MS retention time (method I): t_R = 1.07 min. ^{1}H NMR(400 MHz, Methanol-d4: δ 8.49-8.55 (m, 2H), 7.87 (s, 1H), 7.46 (d, *J* = 8.80 Hz, 1H), 4.27-4.35 (m, 2H), 2.78 (s, 3H), 2.63 (s, 3H), 1.87-1.93 (m, 2H), 1.72-1.77 (m, 1H), 1.55 (s, 3H), 1.02-1.09 (m, 6H) ppm.

Example 480

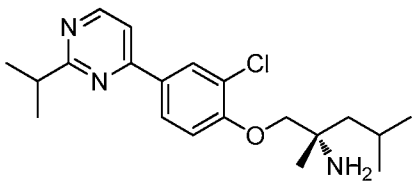
(*S*)-1-(2-chloro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





Part A: (S)-Tert-butyl (1-(2-chloro-4-(2-isopropylpyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-yl) carbamate

A solution of 4-chloro-2-isopropylpyrimidine (0.025 g, 0.160 mmol), (*S*)-*tert*-butyl (1-(2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (prepared as described in Example 285, Part A) (0.075 g, 0.160 mmol), Cs_2CO_3 (0.104 g, 0.319 mmol), and KBr (0.019 g, 0.160 mmol) in 1,4-dioxane (6 mL) was purged with nitrogen gas for 30 min. $PdCl_2$ (dppf)-CH_2Cl_2 adduct (0.013 g, 0.016 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated at 80 °C for 12 h. The reaction mixture was concentrated, dissolved in ethyl acetate (30 mL) and water (30 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (50 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2-chloro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (40 mg, 0.087 mmol, 54% yield) as a brown solid. The solid was taken forward without further purification. LCMS (ESI) *m/e* 462.2 [$(M+H)^+$, calcd for $C_{25}H_{37}ClN_3O_3$ 462.2]; LC/MS retention time (Method A1): t_R = 3.39 min.



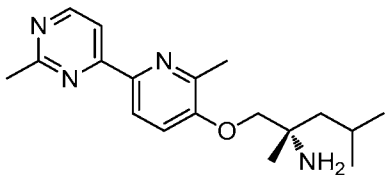
Part B: (S)-1-(2-chloro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

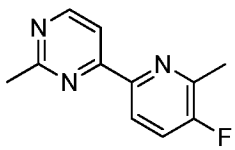
A solution of (*S*)-*tert*-butyl (1-(2-chloro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (0.044 g, 0.095 mmol) in DCM (2

mL) was cooled to 0 °C. TFA (0.147 mL, 1.905 mmol) was added and stirred for 5 min at 0 °C. The reaction mixture was stirred for 4 h at room temperature . The reaction mixture was concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method B) to afford (*S*)-1-(2-chloro-4-(2-isopropylpyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-amine (6 mg, 0.011 mmol, 12% yield) as a pale yellow solid. LCMS (ESI) *m/e* 362.2 [$(M+H)^+$, calcd for $C_{20}H_{29}ClN_3O$ 362.2]; LC/MS retention time (method H): t_R = 2.73 min; LC/MS retention time (method I): t_R = 1.93 min. ^{1}H NMR(400 MHz, Methanol-d4: δ 8.69 (d, *J* = 5.60 Hz, 1H), 8.31-8.34 (m, 1H), 8.18-8.21 (m, 1H), 7.77 (d, *J* = 5.60 Hz, 1H), 7.31 (d, *J* = 8.80 Hz, 1H), 4.19-4.27 (m, 2H), 3.23-3.30 (m, 1H), 1.84-1.91 (m, 2H), 1.69-1.74 (m, 1H), 1.53 (s, 3H), 1.34-1.41 (m, 6H), 1.01-1.08 (m, 6H) ppm.

Example 484

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

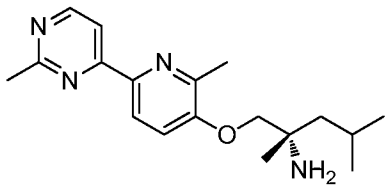




Part A: 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine

A solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), 6-bromo-3-fluoro-2-methylpyridine (148 mg, 0.778 mmol) and 1,1,1,2,2,2-hexamethyldistannane (255 mg, 0.778 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen gas for 10 min. Pd $(Ph_3P)_4$ (90 mg, 0.078 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated in a microwave at 150 °C for 2 h. The reaction mixture was concentrated, dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated, dried over

Na_2SO_4, and concentrated under reduced pressure to afford crude 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine as a brown solid. The solid was purified by silica-gel chromatography (0-40% EtOAc in pet ether) to afford the 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (50 mg, 0.246 mmol, 32% yield) as a off-white solid. LCMS (ESI) *m/e* 204.2 [$(M+H)^+$, calcd for $C_{11}H_{11}FN_3$ 204.1]; LC/MS retention time (Method A1): t_R = 2.12 min.

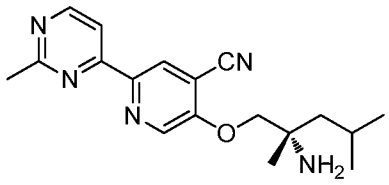


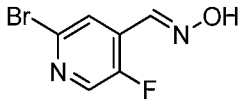
Part B: (S)-2,4-dimethyl-1-(2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yloxy)pentan-2-amine

A solution of (*S*)-2-amino-2,4-dimethylpentan-1-ol (19.37 mg, 0.148 mmol) in THF (4 mL) was cooled to 0 °C. KOtBu (0.443 mL, 0.443 mmol) was added followed by slow addition of (*S*)-2-amino-2,4-dimethylpentan-1-ol (19.37 mg, 0.148 mmol). The reaction mixture was stirred for 5 min at 0 °C and then allowed to stir at 80 °C for 4 h. The reaction mixture was quenched with water (20 mL) and was extracted with ethyl acetate (20 mL). The organic layer was separated out, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method C) to afford (*S*)-2,4-dimethyl-1-(2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yloxy)pentan-2-amine (19 mg, 0.057 mmol, 39% yield) as a pale yellow solid. LCMS (ESI) *m/e* 315.3 [$(M+H)^+$, calcd for $C_{18}H_{27}N_4O$ 315.2]; LC/MS retention time (method H): t_R = 1.24 min; LC/MS retention time (method I): t_R = 0.83 min. ^{1}H NMR(400 MHz, Methanol-d4): δ 8.73 (d, *J* = 5.20 Hz, 1H), 8.39 (d, *J* = 8.80 Hz, 1H), 8.22 (d, *J* = 5.20 Hz, 1H), 7.53 (d, *J* = 8.80 Hz, 1H), 4.16-4.26 (m, 2H), 2.76 (s, 3H), 2.63 (s, 3H), 1.84-1.93 (m, 2H), 1.69-1.75 (m, 1H), 1.51 (s, 3H), 1.01-1.08 (m, 6H) ppm.

Example 487

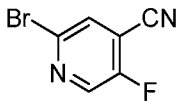
(*S*)-5-(2-amino-2,4-dimethylpentyloxy)-2-(2-methylpyrimidin-4-yl)isonicotinonitrile





Part A: 2-bromo-5-fluoroisonicotinaldehyde oxime

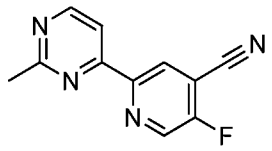
2-Bromo-5-fluoroisonicotinaldehyde (2 g, 9.80 mmol) and hydroxylamine hydrochloride (1.022 g, 14.71 mmol) were dissolved in methanol (20 mL) and water (20 mL). The reaction mixture was heated at 60 °C for 5 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with saturated aqueous sodium bicarbonate solution and was extracted with ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to obtain 2-bromo-5-fluoroisonicotinaldehyde oxime (1.8 g, 8.22 mmol, 84% yield) as an off-white solid which was carried forward without further purification. LCMS (ESI) *m/e* 219.0 [$(M+H)^+$, calcd for $C_6H_5BrFN_2O$ 219.0]; LC/MS retention time (method A1): t_R = 1.63 min.



Part B: 2-bromo-5-fluoroisonicotinonitrile

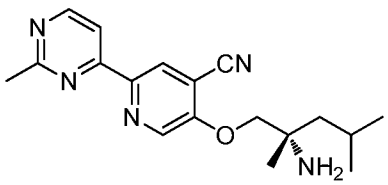
2-Bromo-5-fluoroisonicotinaldehyde oxime (1 g, 4.57 mmol) was taken up in chloroform (20 mL) and cooled to 0 °C. $POCl_3$ (2.128 mL, 22.83 mmol) was added dropwise to the reaction mixture and stirred for 5 min at 0 °C. The reaction mixture was heated at 65 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford a brown colored residue. The residue was diluted with ice-water, basified with saturated aqueous sodium carbonate solution and extracted with ethyl acetate (3 x25 mL). The ethyl acetate layer was dried over Na_2SO_4 and evaporated to afford 2-bromo-5-fluoroisonicotinonitrile (0.8 g, 3.98 mmol, 87 % yield) as a brown

solid that was taken for next step without further purification. ^{1}H NMR 400 MHz, DMSO-d6: δ 8.81 (d, J = 4.40 Hz, 1H), 8.41-8.43 (m, 1H) ppm .



Part C: 5-fluoro-2-(2-methylpyrimidin-4-yl) isonicotinonitrile

A solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), 2-bromo-5-fluoroisonicotinonitrile (156 mg, 0.778 mmol) and 1,1,1,2,2,2-hexamethyldistannane (255 mg, 0.778 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen gas for 10 min. $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated in a microwave at 150 °C for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®). The bed was washed with ethyl acetate (25 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The brown solid was purified by silica gel chromatography (0-40% EtOAc in pet ether) to afford 5-fluoro-2-(2-methylpyrimidin-4-yl) isonicotinonitrile (40 mg, 0.187 mmol, 24% yield) as an off-white color solid. LCMS (ESI) *m/e* 215.2 [$(M+H)^+$, calcd for $C_{11}H_8FN_4$ 215.2]; LC/MS retention time (Method A1): t_R = 1.76 min.



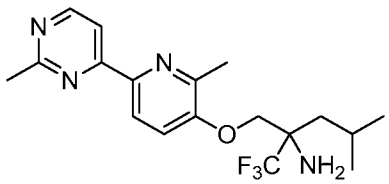
Part D: (S)-5-(2-amino-2, 4-dimethylpentyloxy)-2-(2-methylpyrimidin-4-yl) isonicotinonitrile

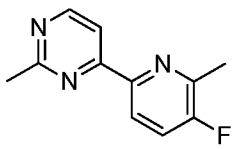
A solution of (*S*)-2-amino-2, 4-dimethylpentan-1-ol (15.31 mg, 0.117 mmol) in DMF (4 mL) was cooled to 0 °C. 5-fluoro-2-(2-methylpyrimidin-4-yl)isonicotinonitrile (25 mg, 0.117 mmol) was added to the reaction mixture followed by portionwise addition of NaH (8.40 mg, 0.350 mmol) and the mixture stirred for 5

min at 0 °C then at 25 °C for 4 h. The reaction mixture was cooled to 0 °C, quenched with water (20 mL) and extracted with ethyl acetate (20 mL). The organic layer was separated out, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by preparative LC/MS (method B) to afford (*S*)-5-(2-amino-2,4-dimethylpentyloxy)-2-(2-methylpyrimidin-4-yl)isonicotinonitrile (4 mg, 9.10umol, 8% yield) as a pale yellow solid. LCMS (ESI) *m/e* 326.2 [$(M+H)^+$, calcd for $C_{18}H_{24}N_5O$ 326.2]; LC/MS retention time (method H): t_R = 2.40 min; LC/MS retention time (method I): t_R = 2.01 min. ^{1}H NMR(400 MHz, Mthanol-d4): δ 8.68 (d, *J* = 5.20 Hz, 1H), 8.64 (d, *J* = 0.40 Hz, 1H), 8.50 (d, *J* = 0.40 Hz, 1H), 8.06 (d, *J* = 5.20 Hz, 1H), 3.57-3.81 (m, 2H), 2.74 (s, 3H), 1.79-1.90 (m, 3H), 1.50 (s, 3H), 0.98-1.02 (m, 6H) ppm.

Example 491

1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine

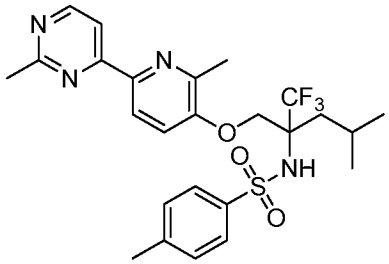




Part A: 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine

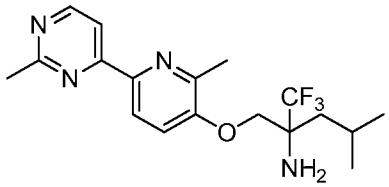
A solution of 4-chloro-2-methylpyrimidine (100 mg, 0.778 mmol), 6-bromo-3-fluoro-2-methylpyridine (148 mg, 0.778 mmol) and 1,1,1,2,2,2-hexamethyldistannane (255 mg, 0.778 mmol) in 1,4-dioxane (2 mL) was purged with nitrogen gas for 20 min. $Pd(Ph_3P)_4$ (90 mg, 0.078 mmol) was added to the reaction mixture and the solution was purged with nitrogen gas again for 10 min. The reaction mixture was heated in a microwave at 150 °C for 2 h. The reaction mixture was concentrated and the residue obtained was dissolved in ethyl acetate (20 mL) and water (20 mL). The biphasic mixture was filtered through diatomaceous earth (Celite®) and the bed was washed with ethyl acetate (25 mL). The ethyl acetate layer

was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a brown colored solid which was purified by silica gel chromatography (0-40% EtOAc in pet ether) to afford 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (42 mg, 0.207 mmol, 27% yield) as an off-white semi-solid. LCMS (ESI) *m/e* 204.2 [$(M+H)^+$, calcd for $C_{11}H_{11}FN_3$ 204.1]; LC/MS retention time (Method A1): t_R =2.41 min.



Part B: 4-methyl-N-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide

A solution of 4-methyl-*N*-(1,1,1-trifluoro-2-(hydroxymethyl)-4-methylpentan-2-yl) benzenesulfonamide (prepare as described in Example 273) (66.8 mg, 0.197 mmol) in DMF (4 mL) was cooled to 0 °C. NaH (14.17 mg, 0.591 mmol) was added to the reaction mixture followed by slow addition of 4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpyrimidine (40 mg, 0.197 mmol) and the mixture stirred for 5 min at 0 °C then at 80 °C for 4 h. The reaction mixture was allowed to cool to room temperature, quenched with water (20 mL) and extracted with ethyl acetate (20 mL). The ethyl acetate layer was separated out ,dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 4-methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide (60 mg, 0.115 mmol, 58% yield) as a brown semi-solid which was taken to next step without further purification. LCMS (ESI) *m/e* 523.2 [$(M+H)^+$, calcd for $C_{25}H_{30}F_3N4O_3S$ 523.2]; LC/MS retention time (Method A1): t_R =2.20 min.

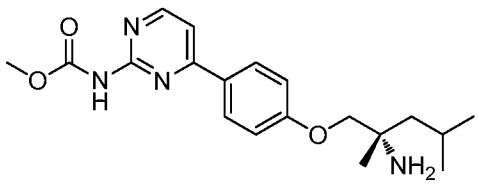


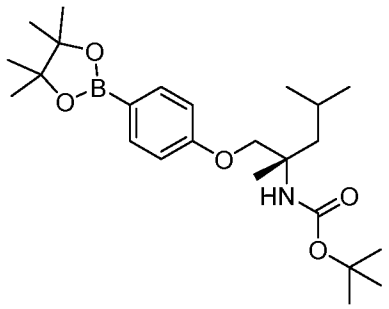
Part C: 1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine

4-Methyl-*N*-(1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-yl)benzenesulfonamide (88 mg, 0.168 mmol) was cooled to 0 °C and sulfuric acid (4 mL, 0.168 mmol) was added dropwise and the reaction mixture stirred for 2 h at 0 °C. The reaction mixture was basified with cold saturated aqueous sodium bicarbonate solution (pH~8-9). The reaction mixture was extracted with ethyl acetate (3x20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by prep LC/MS (method A) to afford 1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine, TFA (11 mg. 0.027 mmol, 16% yield) as a pale yellow solid. LCMS (ESI) *m/e* 369.3 $[(M+H)^+$, calcd for $C_{18}H_{24}F_3N_4O$ 369.2]; LC/MS retention time (method H): t_R = 1.97 min; LC/MS retention time (method I): t_R = 1.19 min. ^{1}H NMR(400 MHz, Methanol-d4): δ 8.69 (d, *J* = 5.60 Hz, 1H), 8.36 (d, *J* = 8.40 Hz, 1H), 8.16 (d, *J* = 5.20 Hz, 1H), 7.49 (d, *J* = 8.80 Hz, 1H), 4.26-4.29 (m, 2H), 2.74 (s, 3H), 2.56 (s, 3H), 1.88-2.03 (m, 2H), 1.73-1.78 (m, 1H), 1.00-1.08 (m, 6H) ppm.

Example 505

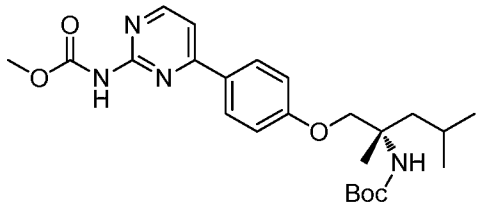
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate





Part A: (S)-tert-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate

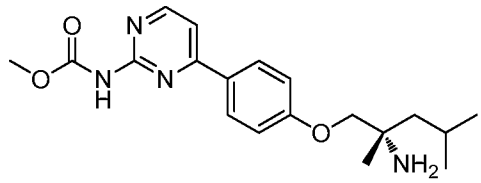
A suspension of (*S*)-*tert*-butyl (1-(4-bromophenoxy)-2,4-dimethylpentan-2-yl)carbamate (2.0 g, 3.47 mmol), bis(pinacolato)diboron (1.321 g, 5.20 mmol), potassium acetate (1.021 g, 10.41 mmol) in 1,4-dioxane (20 ml) was purged with nitrogen for 5 min. PdCl2(dppf)-CH2Cl2 adduct (0.283 g, 0.347 mmol) was added to the reaction mixture under argon and heated to 80 °C (silicon oil bath) for 16 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL), dried over sodium sulfate and concentrated under reduced pressure. The oily residue was purified by silica gel chromatography (0 to 15% of ethyl acetate in hexanes) to afford (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)pentan-2-yl)carbamate (1.49 g, 3.44 mmol, 99 % yield) as a colorless oil. ^{1}H NMR (300MHz, DMSO-d_6) δ 7.59 (d, *J*=8.7 Hz, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 6.54 (br. s., 1H), 4.10 (d, *J*=9.1 Hz, 2H), 3.89 (d, *J*=8.7 Hz, 2H), 1.82 - 1.67 (m, 2H), 1.49 - 1.40 (m, 1H), 1.34 (s, 6H), 1.27 (s, 9H), 1.24 (s, 3H), 1.17 (s, 6H), 0.91 (d, *J*=6.4 Hz, 6H), 0.89 (d, *J*=6.4 Hz, 6H).



Part B: Boc-(S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate

A mixture of methyl (4-chloropyrimidin-2-yl)carbamate (30 mg, 0.160 mmol), (*S*)-*tert*-butyl (2,4-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

yl)phenoxy)pentan-2-yl)carbamate (69.3 mg, 0.160 mmol), cesium carbonate (156 mg, 0.480 mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (6.53 mg, 8.00 µmol) in 1,4-dioxane (1 mL) was heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate (40 mg, 0.087 mmol, 54% yield) as yellow semi-solid. LCMS (ESI) *m/e* 459.3[$(M+H)^+$, calcd for $C_{24}H_{35}N_4O_5$, 459.3]; LC/MS retention time (Method C): t_R = 1.21 min.

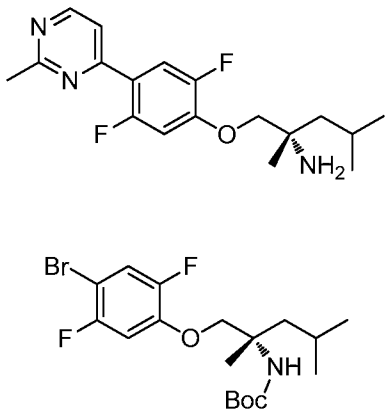


Part B: (S)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate

To a solution of Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate (40 mg, 0.087 mmol) in MeOH at room temperature was added HCl in 1,4-dioxane (436 µl, 1.745 mmol) and the reaction mixture was stirred for 6 h. The reaction mixture diluted with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude material was purified by prep LC/MS (Method A) to afford (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate (16 mg, 0.044 mmol, 51 % yield) as a pale yellow solid. LCMS (ESI) *m/e* 359.3[$(M+H)^+$, calcd for $C_{19}H_{27}N_4O_3$, 359.2]; LC/MS retention time (method D): t_R = 1.02 min LC/MS retention time (Method E): t_R = 0.87 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.42 (d, *J* = 5.60 Hz, 1H), 8.08 (d, *J* = 8.80 Hz, 2H), 7.44 (d, *J* = 5.20 Hz, 1H), 7.00 (d, *J* = 8.80 Hz, 2H), 3.77-3.84 (m, 2H), 3.71 (s, 3H), 1.73-1.79 (m, 1H), 1.43-1.50 (m, 2H), 1.18 (s, 3H), 0.87-0.91 (m, 6H) ppm.

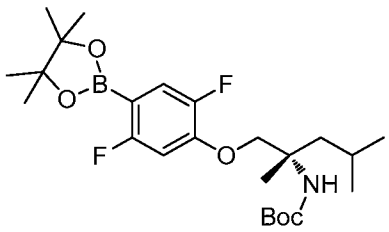
Example 506

(*S*)-1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine



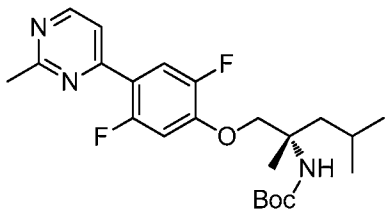
Part A: (S)-tert-butyl (1-(4-bromo-2,5-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a stirred solution of 4-bromo-2,5-difluorophenol (1.425 g, 6.82 mmol) in DMF (20 mL) was added cesium carbonate (6.66 g, 20.45 mmol) and the mixture stirred at RT for 10 min. (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (prepared as described in Example 32, Parts A-E) (2 g, 6.82 mmol) was added and the reaction mixture was heated at 80 °C for 8h. The reaction mixture was cooled to RT and diluted with ethyl acetate (100 mL). The ethyl acetate layer was washed with water (50 mL) and concentrated under reduced pressure to afford a brown oil which was purified by silica gel chromatography (5% EtOAc in hexanes) to afford (*S*)-*tert*-butyl (1-(4-bromo-2,5-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (2 g, 3.79 mmol, 56% yield) as colorless oil. ^{1}H NMR (300 MHz, *CDCl*$_3$): δ 7.27 - 7.23 (m, 1H), 6.88 - 6.81 (m, 1H), 4.60 - 4.52 (m, 1H), 4.23 - 4.15 (m, 1H), 4.04 - 3.98 (m, 1H), 1.91 - 1.76 (m, 2H), 1.51-1.56 (m, 1H), 1.42 - 1.39 (m, 12H), 0.99 (dd, *J*=2.3, 6.4 Hz, 6H) ppm.



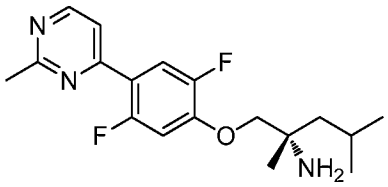
Part B: (S)-tert-butyl (1-(2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a stirred solution of (*S*)-*tert*-butyl (1-(4-bromo-2,5-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (300 mg, 0.710 mmol) in THF (5 mL) at -78 °C was added 1M isopropylmagnesium chloride in THF (0.852 mL, 0.852 mmol) dropwise. The reaction mixture was stirred at -78 °C for 1 h and then 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (145 mg, 0.781 mmol) was added. The mixture was stirred at -78 °C for 1 h then at RT for 3 h. The mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (200 mg, 0.426 mmol, 60% yield) as yellow semi-solid. The crude product obtained was taken into the next step without further purification.



Part C: (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

A mixture of 4-chloro-2-methylpyrimidine (25 mg, 0.194 mmol), (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (91 mg, 0.194 mmol), and cesium carbonate (190 mg, 0.583 mmol) in 1,4-dioxane (1 mL)-water (0.1 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (7.94 mg, 9.72 µmol). The reaction mixture was heated at 100 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (50 mg, 0.100 mmol, 51% yield) as an off-white semi-solid. LCMS (ESI) *m/e* 436.3 [$(M+H)^+$, calcd for $C_{23}H_{32}F_2N_3O_3$, 436.2]; LC/MS retention time (Method C): t_R = 1.29 min.

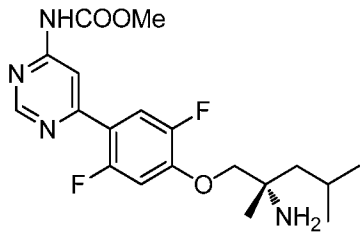


Part D: (*S*)-1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine

To a solution of (*S*)-*tert*-butyl (1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (50 mg, 0.100 mmol) in MeOH (1 mL) at RT was added HCl 4M in 1,4-dioxane (0.250 mL, 0.999 mmol) and the reaction mixture was stirred at RT for 6 h. The reaction mixture diluted with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude material was purified by prep LC/MS (method C) to afford (*S*)-1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (15 mg, 0.044 mmol, 44% yield) as a pale yellow solid. LCMS (ESI) *m/e* 336.2 [$(M+H)^+$, calcd for $C_{18}H_{24}F_2N_3O$, 336.2]; LC/MS retention time (method D): t_R = 2.17 min: LC/MS retention time (Method E): t_R = 1.70 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.68 (d, J = 5.60 Hz, 1H), 8.02-8.06 (m, 1H), 7.73-7.90 (m, 1H), 7.14-7.19 (m, 1H), 4.04-4.12 (m, 2H), 2.74 (s, 3H), 1.82-1.87 (m, 1H), 1.69-1.74 (m, 1H), 1.58-1.63 (m, 1H), 1.38 (s, 3H), 1.03-1.04 (m, 6H) ppm.

Example 507

(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-4-yl)carbamate

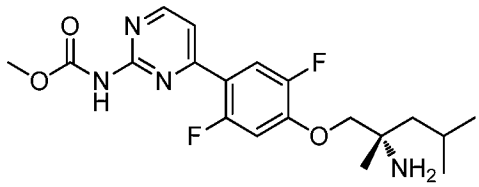


Prepared in a similar fashion as described in Example 304 using (*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-4-yl)carbamate (35 mg, 0.071 mmol) to give (*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-4-yl)carbamate (13 mg, 0.033

mmol, 47% yield) as a pale yellow solid. LCMS (ESI) *m/e* 395.2 [(M+H)$^+$, calcd for $C_{19}H_{25}F_2N_4O_3$, 395.2]; LC/MS retention time (method D): t_R = 2.11 min. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$): δ 8.82 (s, 1H), 8.48-8.49 (m, 1H), 7.91-7.95 (m, 1H), 7.13-7.18 (m, 1H), 3.98-4.04 (m, 2H), 3.84 (s, 3H), 1.85-1.88 (m, 1H), 1.54-1.68 (m, 2H), 1.33 (s, 3H), 1.01-1.05 (m, 6H) ppm.

Example 508

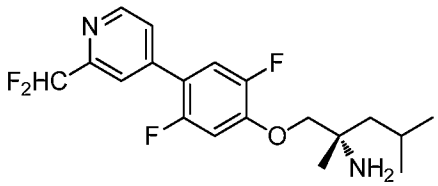
(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-2-yl)carbamate



Prepared in a similar fashion as described in Example 304 using Boc-(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-2-yl)carbamate (40 mg, 0.081 mmol) to give (*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-2-yl)carbamate (8 mg, 0.020 mmol, 25% yield) as a pale yellow solid. LCMS (ESI) *m/e* 395.2 [(M+H)$^+$, calcd for $C_{19}H_{25}F_2N_4O_3$, 395.4]; LC/MS retention time (method D): t_R = 2.00 min. LC/MS retention time (Method E): t_R = 1.70 min. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$): δ 8.59 (d, *J* = 5.20 Hz, 1H), 8.09-8.14 (m, 1H), 7.57-7.58 (m, 1H), 7.10-7.15 (m, 1H), 3.98-4.05 (m, 2H), 3.81 (s, 3H), 1.81-1.86 (m, 1H), 1.63-1.68 (m, 1H), 1.54-1.59 (m, 1H), 1.33 (s, 3H), 1.00-1.03 (m, 6H) ppm.

Example 510

(*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2,5-difluorophenoxy)-2,4-dimethylpentan-2-amine

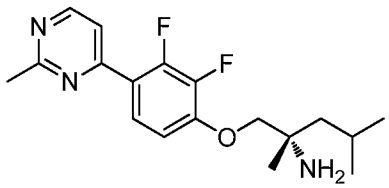


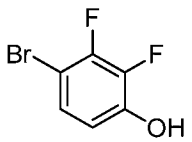
Prepared in a similar fashion as described in Example 506 using (*S*)-*tert*-butyl (1-(4-(2-(difluoromethyl)pyridin-4-yl)-2,5-difluorophenoxy)-2,4-dimethylpentan-2-

yl)carbamate (20 mg, 0.043 mmol) to give (*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2,5-difluorophenoxy)-2,4-dimethylpentan-2-amine (4 mg, 10.48 μmol, 25% yield) as a pale yellow solid. LCMS (ESI) *m/e* 371.2 [$(M+H)^+$, calcd for $C_{19}H_{23}F_4N_2O$, 371.2]; LC/MS retention time (method D): t_R = 2.46 min: LC/MS retention time (Method E): t_R = 2.11 min. ^{1}H NMR (400 MHz, *METHANOL-d4*): δ 8.68-8.93 (m, 1H), 7.87 (s, 1H), 7.73 (t, J = 5.20 Hz, 1H), 7.49-7.54 (m, 1H), 7.13-7.18 (m, 1H), 6.64-6.91 (m, 1H), 3.92-3.99 (m, 2H), 1.80-1.87 (m, 1H), 1.50-1.63 (m, 2H), 1.28 (s, 3H), 0.99-1.02 (m, 6H) ppm.

Example 511

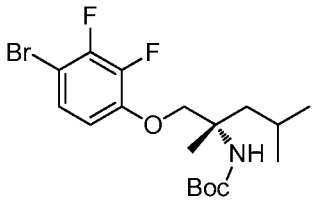
(*S*)-1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine





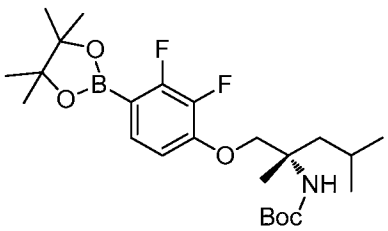
Part A: 4-bromo-2,3-difluorophenol

To a stirred solution of 1-bromo-2,3-difluoro-4-methoxybenzene (3 g, 13.45 mmol) in DCM (30 mL) at -20 °C was added 1M BBr_3 in DCM (26.9 mL, 26.9 mmol) dropwise over 10 min. The cold bath was removed and the reaction mixture was stirred at RT for 12 h. The reaction mixture was cooled to 10 °C and quenched with saturated aqueous sodium bicarbonate solution (100 mL). The mixture was diluted with DCM (150 mL). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure to afford 4-bromo-2,3-difluorophenol (2 g, 9.47 mmol, 70% yield) as a dark red oil. ^{1}H NMR (400 MHz, CHLOROFORM-*d*): δ 7.15-7.21 (m, 1H), 6.69-6.76 (m, 1H), 5.30-5.31 (m, 1H) ppm.



Part B: (*S*)-*tert*-butyl (1-(4-bromo-2,3-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate

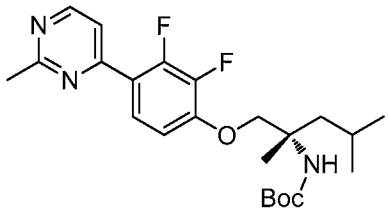
To a solution of 4-bromo-2,3-difluorophenol (50 mg, 0.239 mmol) in DMF (10 mL) was added cesium carbonate (78 mg, 0.239 mmol) and the mixture was stirred at RT for 10 min. (*S*)-*tert*-butyl 4-isobutyl-4-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide, prepared as described in Example 32, Parts A-E (70.2 mg, 0.239 mmol) was added and the mixture heated to 80 °C for 8 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure. 1.5N HCl (10 mL) was added to the residue and the solution was extracted with ethyl acetate (20 mL). The organic layer was separated, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0-15% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-(4-bromo-2,3-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (800 mg, 1.894 mmol, 57% yield) as an off-white semi-solid. ^{1}H NMR (400 MHz, *CHLOROFORM-d*): δ 7.22 - 7.14 (m, 1H), 6.75 - 6.67 (m, 1H), 4.57 - 4.49 (m, 1H), 4.24 - 4.17 (m, 1H), 4.05 - 3.99 (m, 1H), 1.90 - 1.73 (m, 2H), 1.51 - 1.45 (m, 1H), 1.42 - 1.34 (m, 12H), 0.97 (dd, *J*=3.0, 6.5 Hz, 6H) ppm.



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

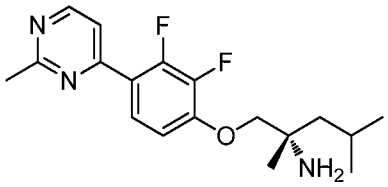
To a solution of (*S*)-*tert*-butyl (1-(4-bromo-2,3-difluorophenoxy)-2,4-dimethylpentan-2-yl)carbamate (500 mg, 1.184 mmol), bis(pinacolato)diboron (361 mg, 1.421 mmol) and potassium acetate (290 mg, 2.96 mmol) in 1,4-dioxane (8 mL) was added $PdCl_2$(dppf)-CH_2Cl_2 adduct (48.3 mg, 0.059 mmol) and the reaction

mixture was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, diluted with brine and extracted with ethyl acetate (20 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford (*S*)-*tert*-butyl (1-(2,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (160 mg, 0.341 mmol, 29% yield) as a colorless semi-solid. The crude product obtained was taken for the next step without further purification.



Part D: (*S*)-*Tert*-butyl (1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate

To a solution of 4-chloro-2-methylpyrimidine (25 mg, 0.194 mmol) and (*S*)-*tert*-butyl (1-(2,3-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (91 mg, 0.194 mmol) in 1,4-dioxane (1 mL) was added cesium carbonate (190 mg, 0.583 mmol) in water (0.1 mL). The reaction mixture was purged with argon for 5 min. $PdCl_2(dppf)\text{-}CH_2Cl_2$ adduct (7.94 mg, 9.72 µmol) was added to and the reaction mixture was heated to 100 °C for 16 h. The reaction mixture was cooled to RT and diluted with ethyl acetate (5 mL). The mixture was filtered through diatomaceous earth (Celite®) and the bed washed with ethyl acetate (5 mL). The filtrate was concentrated under reduced pressure. The residue was purified via silica gel chromatography (40% EtOAc in pet ether) to afford (*S*)-*tert*-butyl (1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (20 mg, 0.046 mmol, 24% yield) as an off-white semi-solid. LCMS (ESI) *m/e* 436.5 $[(M+H)^+$, calcd for $C_{23}H_{32}F_2N_3O_3$, 436.2]; LC/MS retention time (method C): t_R = 2.26 min.



Part E: (*S*)-1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine.

To a stirred solution of (*S*)-*tert*-butyl (1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-yl)carbamate (20 mg, 0.046 mmol) in DCM (0.5 mL) at RT was added HCl 4M in 1,4-dioxane (0.028 mL, 0.918 mmol) and the reaction mixture was stirred at RT for 4 h. The mixture was concentrated under reduced pressure. The crude material was purified by prep LC/MS (method C) to afford (*S*)-1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine (13 mg, 0.038 mmol, 82% yield) as a pale yellow solid. LCMS (ESI) *m/e* 336.2 [$(M+H)^+$, calcd for $C_{17}H_{23}ClN_3O_2$, 336.3]; LC/MS retention time (method D): t_R = 2.28 min: LC/MS retention time (Method E): t_R = 1.01 min. ^{1}H NMR (400 MHz, METHANOL-d_4): δ 8.72 (d, J = 5.60 Hz, 1H), 7.95-8.00 (m, 1H), 7.70-7.71 (m, 1H), 7.18-7.22 (m, 1H), 4.20-4.31 (m, 2H), 2.75 (s, 3H), 1.84-1.89 (m, 1H), 1.69-1.73 (m, 2H), 1.51 (s, 3H), 0.9 (m, 6H) ppm.

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 $MgCl_2$, 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 (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC_{50} 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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
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

Example	AAK1 IC_{50} (nM)
243	1071
244	262
245	11
246	26
247	234
248	74
249	27
250	659
263	950
268	11
273	226
274	986
278	1.9
279	23
280	1.1
285	1.1
290	0.6
297	0.3
298	45
299	195
300	246
301	58
304	298
305	1.0
306	0.6
307	0.9
308	12
309	8.5
310	9.1
311	3.9

Example	AAK1 IC_{50} (nM)
312	4.9
313	2.4
314	1.2
315	1.5
316	8.2
317	103
318	9.7
319	0.5
320	21
323	0.8
324	4.8
325	1.8
326	42
327	0.80
328	0.40
329	2.4
330	7.3
331	45
337	886
343	19
344	26
348	512
349	70
350	39
352	1.4
354	321
355	1.1
356	82
359	865
360	1250

Example	AAK1 IC_{50} (nM)
367	4.5
370	1.4
372	236
373	684
374	339
375	2.6
378	1.4
379	35
382	2.2
383	2.0
384	46
385	50
386	13
387	1008
388	4.7
395	0.7
396	1.6
397	0.7
422	3.5
431	5.4
432	0.7
433	1.8
434	4.7
435	63
436	6.2
437	2.2
438	6.5
439	128
440	308
441	15

Example	AAK1 IC_{50} (nM)
442	19
443	46
444	153
445	62
446	317
447	304
450	126
451	2.7
454	2.4
458	1.5
462	21
465	3.6
469	1.5
474	6.6
479	533
480	18
484	3.2
487	1288
491	789
505	8.7
506	134
507	5.0
508	25
510	19
511	5.1

AAK1 Knockout Mice

Mice homozygous (-/-) for the disruption of the AAK1 gene were prepared by two methods; gene trapping and homologous recombination.

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 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 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 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.

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 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;

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)).

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 µl 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 selected from

(*R*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine;

(*S*)-2,4-dimethyl-1-((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine;

methyl 5-(2-amino-4-methyl-2-(trifluoromethyl)pentyloxy)-6-methyl-2,4'-bipyridin-2'-ylcarbamate;

1,1,1-trifluoro-4-methyl-2-(((3-methyl-5-(2-methylpyrimidin-4-yl)pyridin-2-yl)oxy)methyl)pentan-2-amine;

(*S*)-6-(4-((2-amino-2, 4-dimethylpentyl) oxy)-3-(trifluoromethyl) phenyl) pyrimidin-4-amine;

(*S*)-1-((2-(fluoromethyl)-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

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

(*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-4-amine;

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

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-amine;

(*S*)-2,4-dimethyl-1-((5-(2-methylpyrimidin-4-yl)-3-(oxazol-5-yl)pyridin-2-yl)oxy)pentan-2-amine;

(*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-4-(oxazol-5-yl)pyridin-3-yl)oxy)pentan-2-amine;

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

(*S*)-methyl (5-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyridazin-3-yl)carbamate;

(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate;

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

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

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-2-yl)carbamate;

(*S*)-1-(2-chloro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-(4-(6-methylpyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

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

(*S*)-isopropyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate;

(*S*)-methyl (4-(5-((2-amino-2,4 dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-yl)carbamate;

(*S*)-4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-2-amine;

(*S*)-ethyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-2-yl)carbamate;

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

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

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3 (trifluoromethyl)phenyl)pyrimidin-2-ol;

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

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

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

(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(difluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate;

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

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

2',6-bis(difluoromethyl)-5-((2-isobutylazetidin-2-yl)methoxy)-2,4'-bipyridine;

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

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)benzonitrile;

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

(*S*)-2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)pentan-2-amine;

(*S*)-1-(2-fluoro-4-(2-(trifluoromethyl)pyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

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

(*S*)-6-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-methylpyridin-2-yl)pyrimidin-4-amine;

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

(*S*)-2,4-dimethyl-1-((6-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine;

(*S*)-2,4-dimethyl-1-((4-methyl-2'-(trifluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)pentan-2-amine;

(*S*)-1-(2-(difluoromethyl)-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-(2-(fluoromethyl)-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*R*)-2,4-dimethyl-1-((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)pentan-2-amine;

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

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

(*S*)-2,4-dimethyl-1-(5-methyl-2-(pyridin-4-yl)thiazol-4-yloxy)pentan-2-amine;

1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine;

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

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

(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate;

(*R*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-fluoropyridin-3-yl)pyrimidin-2-yl)carbamate;

(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-4-methylpyridin-3-yl)pyrimidin-2-yl)carbamate;

(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-2-yl)carbamate;

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

(*S*)-methyl (4-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-2-yl)carbamate;

(*S*)-1-(2-chloro-4-(2-chloropyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

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

(*S*)-2,4-dimethyl-1-(2-methyl-4-(6-methylpyrimidin-4-yl)phenoxy)pentan-2-amine;

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

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

(*S*)-1-((2-(fluoromethyl)-6-(6-methylpyrimidin-4-yl)pyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-methyl (4-(5-((2-amino-2,4-dimethylpentyl)oxy)-6-(fluoromethyl)pyridin-2-yl)pyrimidin-2-yl)carbamate;

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

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

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

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-5-methylisoxazole-3-carboxamide;

(*S*)-*N*-(4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyridin-2-yl)-5-isopropyl-1*H*-pyrazole-3-carboxamide;

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-*N*-(pyridin-3-ylmethyl)pyridin-2-amine;

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-*N*-(furan-2-ylmethyl)pyridin-2-amine;

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)-*N*-(benzo[*d*][1,3]dioxol-5-yl)pyridin-2-amine;

(*S*)-4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-fluorophenyl)-6-methyl-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-one;

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

(*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-amine;

(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-(trifluoromethyl)phenyl)pyrimidin-4-yl)carbamate;

(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-4-yl)carbamate;

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-methylphenyl)pyrimidin-2-yl)carbamate;

(*S*)-1-(2,5-difluoro-4-(6-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methylpyrimidin-4-yl)benzonitrile;

(*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-chloropyridin-3-yl)pyrimidin-4-yl)carbamate;

(*S*)-methyl (6-(6-((2-amino-2,4-dimethylpentyl)oxy)-5-methylpyridin-3-yl)pyrimidin-4-yl)carbamate;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-methoxypyrimidin-4-yl)benzonitrile;

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

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-chloropyrimidin-4-yl)benzonitrile;

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

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-ethylpyrimidin-4-yl)benzonitrile;

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

(*S*)-1-((3-chloro-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-((3-methyl-5-(6-methylpyrimidin-4-yl)pyridin-2-yl)oxy)pentan-2-amine;

(*S*)-1-((5-(6-ethylpyrimidin-4-yl)-3-methylpyridin-2-yl)oxy)-2,4-dimethylpentan-2-amine;

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

(*S*)-1-((6-(2-chloropyrimidin-4-yl)-2-methylpyridin-3-yl)oxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-((6-(2-methylpyrimidin-4-yl)-2-(trifluoromethyl)pyridin-3-yl)oxy)pentan-2-amine;

(*S*)-2-(2-amino-2, 4-dimethylpentyloxy)-5-(2-methylpyrimidin-4-yl) benzonitrile;

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

(*S*)-1-(2-chloro-4-(2-(trifluoromethyl) pyrimidin-4-yl) phenoxy)-2, 4-dimethylpentan-2-amine;

(*S*)-1-(2-chloro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2-(2-amino-2,4-dimethylpentyloxy)-5-(2-(trifluoromethyl)pyrimidin-4-yl)benzonitrile;

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

(*S*)-1-(2-chloro-4-(2-isopropylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-(4-(2-methylthieno[2,3-*d*]pyrimidin-4-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

(*S*)-1-(2-chloro-4-(2-cyclopropylpyrazolo[1,5-*a*]pyrimidin-7-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-(4-(2-cyclopropylpyrazolo[1,5-*a*]pyrimidin-7-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-(2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yloxy)pentan-2-amine;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidin-7-yl)benzonitrile;

(*S*)-5-((2-amino-2,4-dimethylpentyl)oxy)-2-(pyrazolo[1,5-*a*]pyrimidin-7-yl)isonicotinonitrile;

(*S*)-5-(2-amino-2,4-dimethylpentyloxy)-2-(2-methylpyrimidin-4-yl)isonicotinonitrile;

(*S*)-2,4-dimethyl-1-((2-methyl-6-(pyrazolo[1,5-*a*]pyrimidin-7-yl)pyridin-3-yl)oxy)pentan-2-amine;

(*S*)-1-(2,5-difluoro-4-(pyrazolo[1,5-*a*]pyrimidin-7-yl)phenoxy)-2,4-dimethylpentan-2-amine;

1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(pyrazolo[1,5-*a*]pyrimidin-7-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine;

1,1,1-trifluoro-4-methyl-2-(((2-methyl-6-(2-methylpyrimidin-4-yl)pyridin-3-yl)oxy)methyl)pentan-2-amine;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-methylimidazo[1,2-*b*]pyridazin-8-yl)benzonitrile;

(*S*)-1-(4-(2-cyclopropylimidazo[1,2-*b*]pyridazin-8-yl)-2-fluorophenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(6-chloro-2-cyclopropylimidazo[1,2-*b*]pyridazin-8-yl)benzonitrile;

(*S*)-1-(4-(6-chloro-2-methylimidazo[1,2-*b*]pyridazin-8-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-(4-(6-chloro-2-cyclopropylimidazo [1,2-*b*]pyridazin-8-yl)-2-(trifluoromethyl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-(2-fluoro-4-(2-methylimidazo[1,2-*b*]pyridazin-8-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-2,4-dimethyl-1-(4-(2-methylimidazo[1,2-*b*]pyridazin-8-yl)-2-(trifluoromethyl)phenoxy)pentan-2-amine;

(*S*)-2-((2-amino-2,4-dimethylpentyl)oxy)-5-(2-cyclopropylimidazo[1,2-*b*]pyridazin-8-yl)benzonitrile;

(*S*)-2,4-dimethyl-1-(2-methyl-4-(2-(trifluoromethyl)imidazo[1,2-*b*]pyridazin-8-yl)phenoxy)pentan-2-amine;

(*S*)-2,4-dimethyl-1-(4-(2-(trifluoromethyl)imidazo[1,2-*b*]pyridazin-8-yl)phenoxy)pentan-2-amine;

(*S*)-1-(4-(imidazo[1,2-*b*]pyridazin-3-yl)-2-methylphenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-1-(2-chloro-4-(imidazo[1,2-*b*]pyridazin-3-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*R*)-2,4-dimethyl-1-((3-methyl-5-(2-(trifluoromethyl)imidazo[1,2-*b*]pyridazin-8-yl)pyridin-2-yl)oxy)pentan-2-amine;

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)phenyl)pyrimidin-2-yl)carbamate;

(*S*)-1-(2,5-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

(*S*)-methyl (6-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-4-yl)carbamate;

(*S*)-methyl (4-(4-((2-amino-2,4-dimethylpentyl)oxy)-2,5-difluorophenyl)pyrimidin-2-yl)carbamate;

(*S*)-6-(4-((2-amino-2,4-dimethylpentyl)oxy)-3-chlorophenyl)pyrimidin-4(3*H*)-one;

(*S*)-1-(4-(2-(difluoromethyl)pyridin-4-yl)-2,5-difluorophenoxy)-2,4-dimethylpentan-2-amine; and

(*S*)-1-(2,3-difluoro-4-(2-methylpyrimidin-4-yl)phenoxy)-2,4-dimethylpentan-2-amine;

or a pharmaceutically acceptable salt thereof.

2. A composition comprising a pharmaceutically acceptable amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

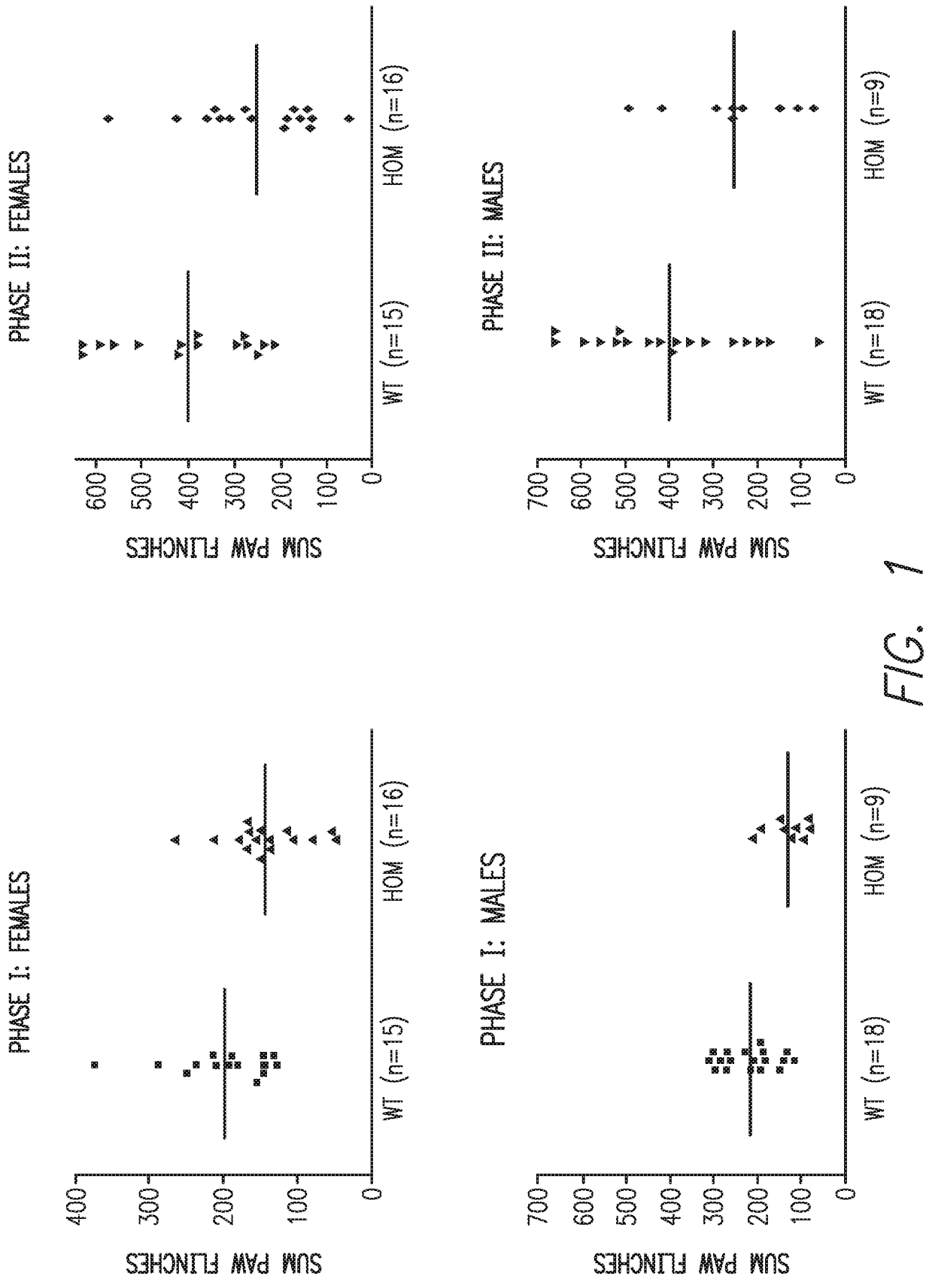
3. A method of inhibiting adaptor associated kinase 1 (AAK1) activity, comprising contacting AAK1 with a compound of claim 1,or a pharmaceutically acceptable salt thereof.

4. A method for treating or managing a disease or a disorder mediated by AAK1activity, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

5. The method of claim 4, wherein the disease or disorder is selected from Alzheimer's disease, bipolar disorder, pain, Parkinson's disease, and schizophrenia.

6. The method of claim 5 wherein the pain is neuropathic pain.

7. The method of claim 6 wherein the neuropathic pain is fibromyalgia or peripheral neuropathy.


PHASE II: FEMALES
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100
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HOM (n=16)
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500
400
300
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100
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PHASE I: FEMALES
SUM PAW FLINCHES
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WT (n=15)
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PHASE I: MALES
SUM PAW FLINCHES
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600
500
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100
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WT (n=18)
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FIG. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/054471

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D213/75 C07D239/42 C07D401/14 C07D413/14
C07D213/73 C07D213/85 C07D237/20 C07D239/26 C07D239/30
C07D239/34 C07D471/04 C07D213/26 C07D213/61 C07D213/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/134036 A1 (SQUIBB BRISTOL MYERS CO [US]) 12 September 2013 (2013-09-12) claims 1,6-13; examples	1-7
A	WO 2014/022167 A1 (SQUIBB BRISTOL MYERS CO [US]) 6 February 2014 (2014-02-06) claims 1,5-12; examples	1-7
X,P	WO 2015/153720 A1 (SQUIBB BRISTOL MYERS CO [US]) 8 October 2015 (2015-10-08) claims 1-15; examples	1-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 January 2017	03/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Ladenburger, Claude

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/054471

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