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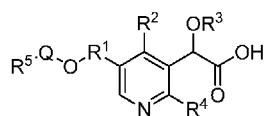
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(54) Title: PYRIDIN-3-YL ACETIC ACID DERIVATIVES AS INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION



(I)

(57) Abstract: Disclosed are compounds of Formula (I), including pharmaceutically acceptable salts, pharmaceutical compositions comprising the compounds, methods for making the compounds and their use in inhibiting HIV integrase and treating those infected with HIV or AIDS.

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PYRIDIN-3-YL ACETIC ACID DERIVATIVES AS INHIBITORS OF HUMAN
IMMUNODEFICIENCY VIRUS REPLICATION

FIELD OF THE INVENTION

5 The invention relates to compounds, compositions, and methods for the treatment of human immunodeficiency virus (HIV) infection. More particularly, the invention provides novel inhibitors of HIV, pharmaceutical compositions containing such compounds, and methods for using these compounds in the treatment of HIV infection. The invention also relates to methods for making the compounds hereinafter described.

10 BACKGROUND OF THE INVENTION

 Current therapy for HIV-infected individuals consists of a combination of approved anti-retroviral agents. Over two dozen drugs are currently approved for HIV infection, either as single agents or as fixed dose combinations or single tablet regimens, the latter
15 two containing 2-4 approved agents. These agents belong to a number of different classes, targeting either a viral enzyme or the function of a viral protein during the virus replication cycle. Thus, agents are classified as either nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INIs), or entry inhibitors (one, maraviroc, targets the host CCR5
20 protein, while the other, enfuvirtide, is a peptide that targets the gp41 region of the viral gp160 protein). In addition, a pharmacokinetic enhancer with no antiviral activity, i.e., cobicistat, available from Gilead Sciences, Inc. under the tradename TYBOST™ (cobicistat) tablets, has recently been approved for use in combinations with certain antiretroviral agents (ARVs) that may benefit from boosting.

25 In the US, where combination therapy is widely available, the number of HIV-related deaths has dramatically declined (Palella, F. J.; Delany, K. M.; Moorman, A. C.; Loveless, M. O.; Furher, J.; Satten, G. A.; Aschman, D. J.; Holmberg, S. D. *N. Engl. J. Med.* 1998, 338, 853-860).

30 Unfortunately, not all patients are responsive and a large number fail this therapy. In fact, initial studies suggest that approximately 30-50% of patients ultimately fail at least one drug in the suppressive combination. Treatment failure in most cases is caused by the emergence of viral resistance. Viral resistance in turn is caused by the replication rate of

HIV-1 during the course of infection combined with the relatively high viral mutation rate associated with the viral polymerase and the lack of adherence of HIV-infected individuals in taking their prescribed medications. Clearly, there is a need for new antiviral agents, preferably with activity against viruses already resistant to currently approved drugs. Other important factors include improved safety and a more convenient dosing regimen than many of the currently approved drugs.

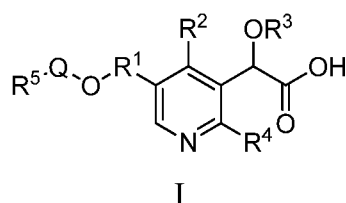
Compounds which inhibit HIV replication have been disclosed. See, for example, the following patent applications: WO2007131350, WO2009062285, WO2009062288, WO2009062289, WO2009062308, WO2010130034, WO2010130842, WO2011015641, WO2011076765, WO2012033735, WO2013123148, WO2013134113, WO2014164467, WO2014159959, WO2015126726, and WO2017025915.

Allosteric Integrase Inhibitors useful for treating HIV are disclosed, for example, in PCT/IB2018/050022 and PCT/IB2018/050021.

What is now needed in the art are additional compounds which are novel and useful in the treatment of HIV. Additionally, these compounds may desirably provide advantages for pharmaceutical uses, for example, with regard to one or more of their mechanisms of action, binding, inhibition efficacy, target selectivity, solubility, safety profiles, or bioavailability.

BRIEF DESCRIPTION OF THE INVENTION

Briefly, in one aspect, the present invention discloses compounds of Formula I, or a pharmaceutically acceptable salt thereof,



wherein R³ is C₁₋₈alkyl;

R⁴ is C₁₋₄alkyl;

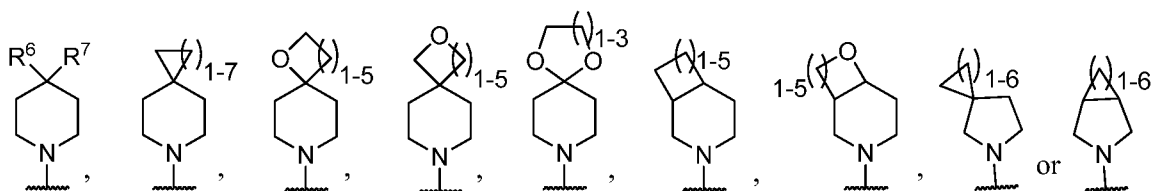
R¹ is pyridinyl or phenyl and is optionally substituted with 1 or 2 halogens;

Q is C₁₋₆alkyl optionally substituted with 1 to 3 halogens;

R⁵ is H, phenyl, phenyl-O-, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-O-, C₁₋₆alkyl-O-, pyrazolyl,

tetrahydropyranyl, or tetrahydrofuran, and is optionally substituted with 1-3 substituents independently selected from halogen and C₁₋₆alkyl;

R² is



wherein R⁶ is C₁₋₆alkyl; R⁷ is C₂₋₆alkyl, phenyl, -OC₁₋₆alkyl, CN, or halogen; and R² is optionally substituted with 1-3 substituents independently selected from halogen and C₁₋₆alkyl.

The invention also provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

The invention also provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of HIV infection

The invention also provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of HIV infection.

The invention also provides a pharmaceutical composition comprising a compound or salt of the invention.

In addition, the invention provides a method of treating HIV infection comprising administering a compound or salt of the invention to a patient.

In addition, the invention provides a method for inhibiting HIV integrase.

Also provided in accordance with the invention are methods for making the compounds and salts of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Preferably R³ is C₃₋₅alkyl.

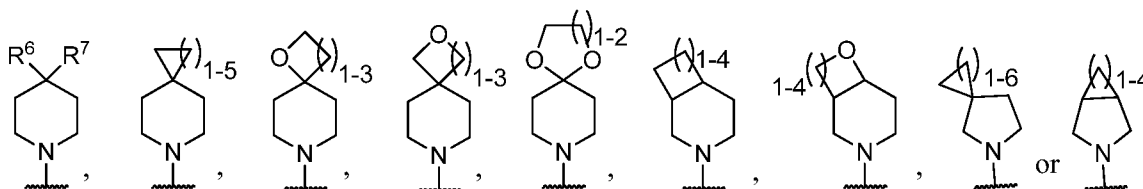
Preferably R⁴ is methyl or ethyl.

Preferably R¹ is pyridinyl and is optionally substituted with a fluorine.

Preferably Q is C₁₋₆alkyl optionally substituted with 1-3 fluorines.

Preferably R⁵ is optionally substituted with 1-3 substituents independently selected from F, Cl, and methyl.

Preferably R² is



wherein R^6 is methyl; R^7 is C_{2-3} alkyl, phenyl, OCH_3 , CN, or F; and is optionally substituted with 1-2 substituents independently selected from F and CH_3 .

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

Some of the compounds of the invention exist in stereoisomeric forms. The invention includes all stereoisomeric forms of the compounds including enantiomers and diastereomers. Methods of making and separating stereoisomers are known in the art. The invention includes all tautomeric forms of the compounds. The invention includes atropisomers and rotational isomers.

In one embodiment, a method for treating or preventing an HIV infection in a patient having or at risk of having the infection is provided, comprising administering to the patient a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents.

In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided.

In one embodiment, pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or

more additional therapeutic agents, and a pharmaceutically acceptable carrier, diluent or excipient are provided. Preferred compositions include tablets and parenteral formulations.

In one embodiment, combination pharmaceutical agents comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in combination with one or
5 more additional therapeutic agents are provided.

In the above embodiments, the additional therapeutic agent may be an anti-HIV agent. For example, in some embodiments, the additional therapeutic agent is selected from the group consisting of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors
10 of reverse transcriptase, HIV integrase inhibitors, HIV non-catalytic site (or allosteric) integrase inhibitors, entry inhibitors (e.g., CCR5 inhibitors, gp41 inhibitors (i.e., fusion inhibitors) and CD4 attachment inhibitors), CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, compounds that target the HIV capsid ("capsid inhibitors"; e.g., capsid polymerization inhibitors or capsid disrupting compounds such as those disclosed in
15 WO 2013/006738 (Gilead Sciences), US 2013/0165489 (University of Pennsylvania), and WO 2013/006792 (Pharma Resources), pharmacokinetic enhancers, and other drugs for treating HIV, and combinations thereof.

"Combination," "coadministration," "concurrent" and similar terms referring to the administration of a compound of Formula I with at least one anti-HIV agent mean that the
20 components are part of a combination antiretroviral therapy or highly active antiretroviral therapy ("HAART") as understood by practitioners in the field of AIDS and HIV infection.

"Patient" means a person infected with the HIV virus.

"Treatment," "therapy," "regimen," "HIV infection," "ARC," "AIDS" and related terms are used as understood by practitioners in the field of AIDS and HIV infection.

Those terms not specifically set forth herein shall have the meaning which is
25 commonly understood and accepted in the art.

Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of about 1-100 milligram per milliliter ("mg/mL"). Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL,
30 and 100 mg/mL. Generally, other antiretroviral agents will be present in a unit range similar to agents of that class used clinically. Typically, this is about 1-100 mg/mL.

The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred.

Methods of Synthesis

The compounds of this invention can be made by various methods known in the art including those of the following schemes and in the specific embodiments section. The structure numbering and variable numbering shown in the synthetic schemes are distinct from, and should not be confused with, the structure or variable numbering in the claims or the rest of the specification. The variables in the schemes are meant only to illustrate how to make some of the compounds of this invention. The disclosure is not limited to the foregoing illustrative examples and the examples should 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.

Abbreviations used in the schemes and examples generally follow conventions used in the art. Chemical abbreviations used in the specification and examples are defined as follows: "KHMDS" for potassium bis(trimethylsilyl)amide; "DMF" for N,N-dimethylformamide; "HATU" for O-(t-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, "MeOH" for methanol; "Ar" for aryl; "TFA" for trifluoroacetic acid, "DMSO" for dimethylsulfoxide; "h" for hours; "rt" for room temperature or retention time (context will dictate); "min" for minutes; "EtOAc" for ethyl acetate; "THF" for tetrahydrofuran; "Et₂O" for diethyl ether; "DMAP" for 4-dimethylaminopyridine; "DCE" for 1,2-dichloroethane; "ACN" for acetonitrile; "DME" for 1,2-dimethoxyethane; "HOBt" for 1-hydroxybenzotriazole hydrate; and "DIEA" for diisopropylethylamine.

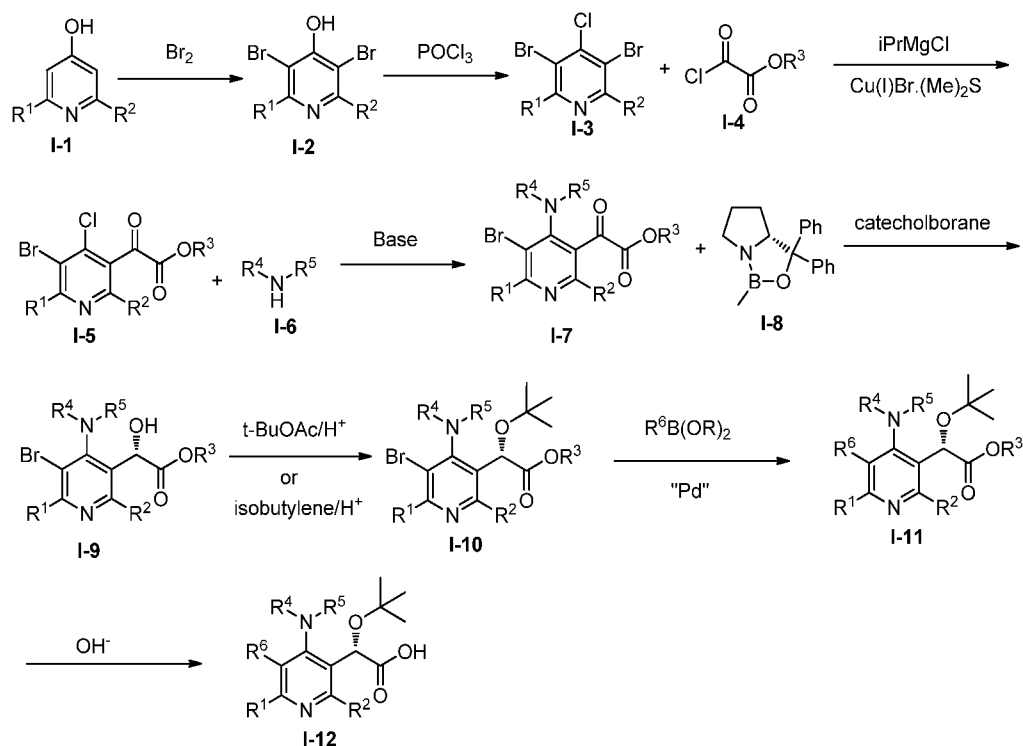
Certain other abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "μL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "sat" or "sat'd" for saturated, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography,

“RP HPLC” for reverse phase HPLC, “TLC” or “tlc” for thin layer chromatography, “NMR” for nuclear magnetic resonance spectroscopy, “¹H” for proton, “δ” for delta, “s” for singlet, “d” for doublet, “t” for triplet, “q” for quartet, “m” for multiplet, “br” for broad, “Hz” for hertz, and “α”, “β”, “R”, “S”, “E”, and “Z” are stereochemical designations

5 familiar to one skilled in the art.

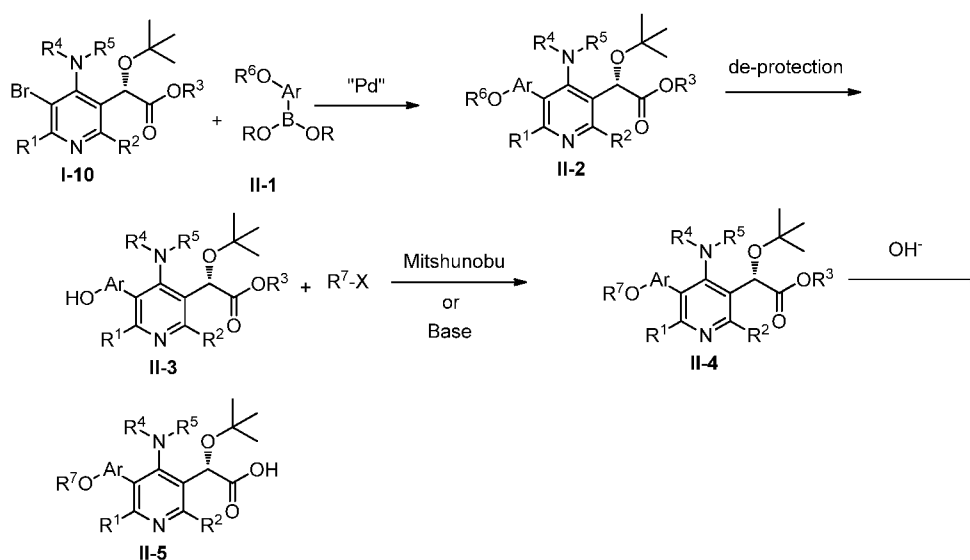
Some compounds can be synthesized from an appropriately substituted heterocycle **I-1** according to Scheme I. Compounds **I-1** and **I-6** are commercially available or synthesized by reactions well known in the art. Treatment of compound **I-1** with bromine provided the dibromo intermediates **I-2** which was converted to the chloropyridine **I-3** by
10 reacting with POCl₃. Intermediate **I-3** conveniently transformed to ketoester **I-5** using conditions well-known to those skilled in the art, including reacting **I-3** with Grignard reagent in the presence of catalytic copper(I) bromide dimethylsulfide complex followed by alkyl 2-chloro-2-oxoacetate. Coupling of amines **I-5** with intermediate **I-6** in the presence of an organic base such as Hunig’s base provided intermediate **I-7**. Chiral Lewis
15 acid such as **I-8** mediated reduction of ketoester **I-7** with catecholborane furnished the chiral alcohol **I-9**. Tertiary butylation of alcohol **I-9** by well-known conditions, including but not limited to tertiary-butyl acetate and perchloric acid, gave intermediate **I-10**. Intermediates **I-10** are conveniently transformed to intermediates **I-11** using conditions well-known in the art, including but not limited to the Suzuki coupling between
20 intermediates **I-10** and R⁶B(OR)₂. The boronate or boronic acid coupling reagents, well-known in the art, are commercially available or are prepared by reactions well-known to those skilled in the art. Hydrolysis of intermediate **I-11** by using conditions well-known to those skilled in the art furnished the carboxylic acid **I-12**.

Scheme I



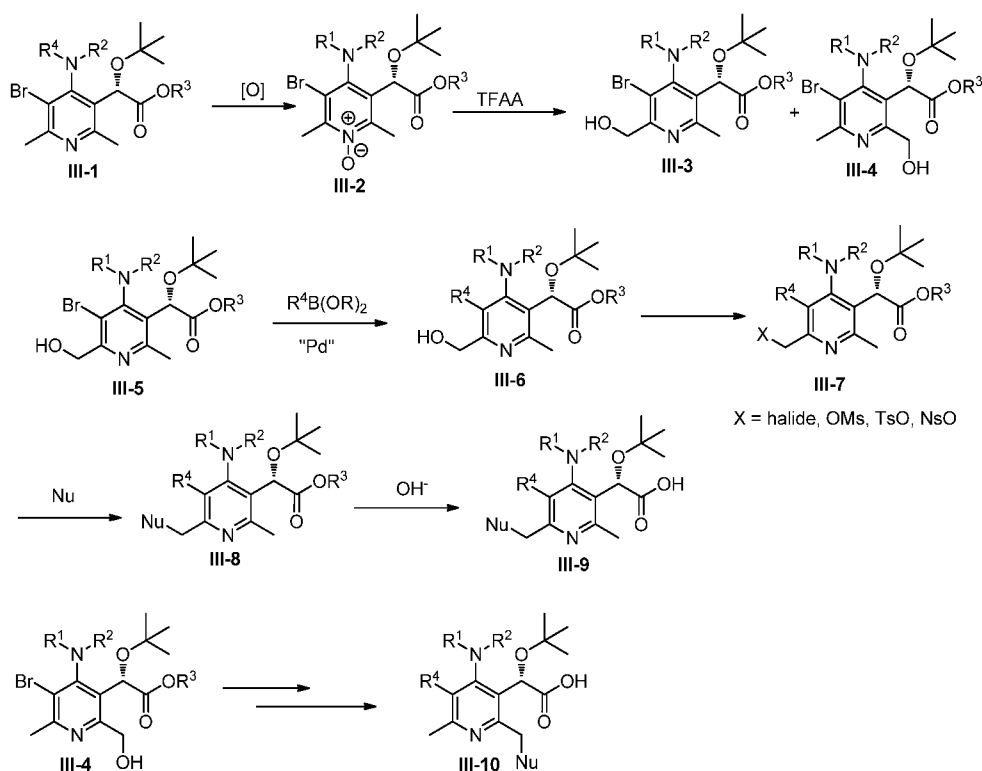
Intermediates **I-10** are conveniently transformed to intermediates **II-2** using conditions well-known in the art, including but not limited to the Suzuki coupling between intermediates **I-10** and **II-1**. Cleavage of protecting group in **II-2** provided phenol **II-3**. Alkylation of the phenol **II-3** was achieved by using conditions well known to those skilled in the art, including but not limited to Mitsunobu reaction to provide the intermediate **II-4**. Hydrolysis of intermediate **II-4** by using conditions well-known in the literature furnished carboxylic acid **II-5**.

Scheme II



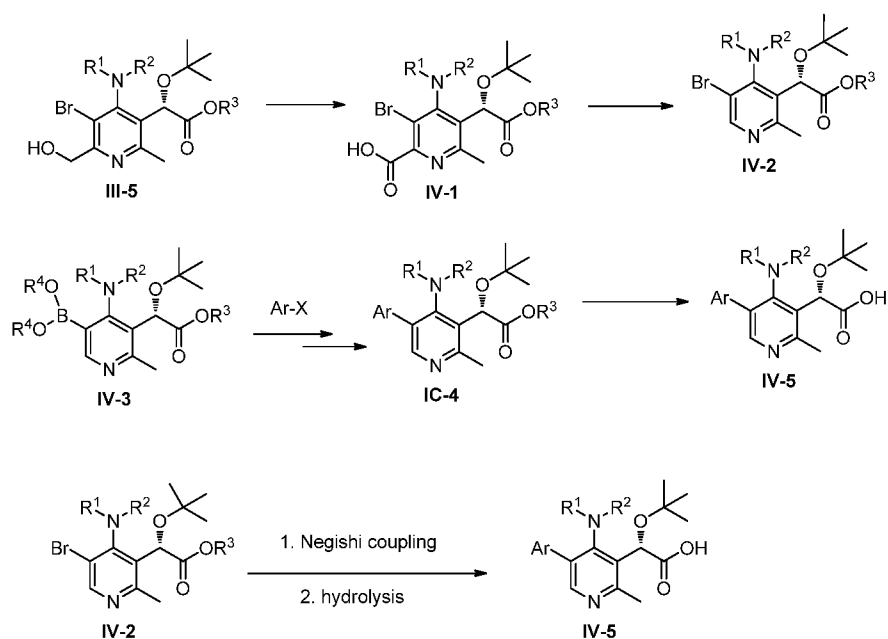
In yet another method, some compounds of this invention can be synthesized according to Scheme III. Pyridine **III-1**, can be produced using methods similar to those described in the previous schemes. This intermediate can be carried on to the final products by a variety of paths. In one, the C2 and C6 alkyl groups can be oxidized to furnish intermediates **III-3** and/or **III-4** which can be further transformed to final compounds **III-9** or **III-10** by methods well known in the art.

Scheme III



In yet another process, some compounds of this invention can be synthesized according to Scheme IV. Pyridine **III-5** can be transformed to the final products by several paths. In one path, the C6 hydroxymethyl is oxidized to furnish carboxylic acid **IV-1** which upon heating in the presence of acid provided C6-desmethyl analog **IV-2**. The “Pd” mediated coupling of boronate **IV-2** with appropriate aryl halides or aryl triflate followed by hydrolysis furnished the target compounds. Alternatively, the target compounds could be synthesized by coupling intermediate **IV-2** with aryl halides under Negishi coupling conditions followed by ester hydrolysis.

Scheme IV



The compounds described herein were purified by the methods well known to those skilled in art by normal phase column chromatography on silica gel column using appropriate solvent system described. Preparative HPLC or preparative LC/MS purifications mentioned in this experimentation section were carried out by gradient elution either on Sunfire Prep C18 ODB column (5 μ m; 19 or 30 X 100 mm) or Waters Xbridge C18 column (5 μ M; 19 X 200 or 30 X 100 mm) or Water Atlantis (5 μ m; 19 or 30 X 100 mm) or Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles using the following mobile phases. Mobile phase A: 9:1 H₂O/acetonitrile with 10 mM NH₄OAc and mobile phase B: A: 9:1 acetonitrile/H₂O with 10 mM NH₄OAc; or mobile phase A: 9:1 H₂O/acetonitrile with 0.1% TFA and mobile phase B: A: 9:1 acetonitrile/H₂O with 0.1% TFA; or mobile phase A: water/MeOH (9:1) with 20 mM NH₄OAc and mobile phase B: 95:5 MeOH/H₂O with 20 mM NH₄OAc or mobile phase A: water/MeOH (9:1) with 0.1% TFA and mobile phase B: 95:5 MeOH/H₂O with 0.1% TFA or mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate.

Analysis Methods:

LCMS Method 1: Column: Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C;

Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

LCMS Method 2: Column: Waters XBridge C18, 2.1 mm x 50 mm, 1.7 μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.1 % trifluoroacetic acid; Temperature: 50 $^{\circ}$ C; Gradient: 0 %B to 100 %B over 3 min, then a 0.75 min hold at 100 %B; Flow: 1 mL/min; Detection: MS and UV (220 nm).

LCMS Method 3: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7- μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 $^{\circ}$ C; Gradient: 0-100% B over 3 minutes, then a 0.75-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

LCMS Method 4: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7- μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 0.05 % trifluoroacetic acid; Mobile Phase B: 95:5 acetonitrile:water with 0.05 % trifluoroacetic acid; Temperature: 40 $^{\circ}$ C; Gradient: 0 %B to 100 %B over 1.5 min, then a 0.5 min hold at 100 %B; Flow: 0.8 mL/min; Detection: MS and UV (220 nm).

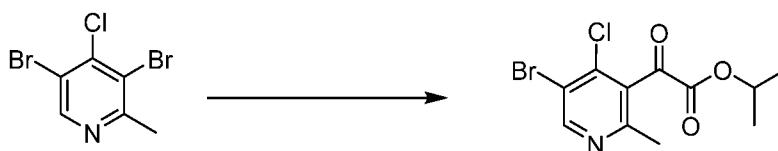
LCMS Method 5: Column: Phenomenex Luna C18, 2.0 x 30 mm, 3- μ m particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 40 $^{\circ}$ C; Gradient: 0-100% B over 2 minutes, then a 1-minute hold at 100% B; Flow: 1.0 mL/min; Detection: UV at 220 nm.



To a stirred solution of 2-methylpyridin-4-ol (8.0 g, 73 mmol) in dichloromethane (90 ml) and MeOH (11 ml) was added tert-butylamine (15.7 ml, 148 mmol) and the mixture was cooled to 0 $^{\circ}$ C. Bromine (7.55 ml, 147 mmol) was added dropwise over a 20 minute period. The reaction mixture was stirred at rt for 2 hours. Then the resulting slurry was filtered through a buchner funnel and the solid was washed with methanol (100 ml) and dried overnight to afford 3,5-dibromo-2-methylpyridin-4-ol (10 g, 37.5 mmol, 51.1 % yield). LCMS Method 4: retention time = 0.704 min.; observed ion = 267.8. 1 H NMR (500 MHz, DMSO- d_6) δ 12.33 (br s, 1H), 8.21 (s, 1H), 2.40 (s, 3H).



To a solution of 3,5-dibromo-2-methylpyridin-4-ol (13.5 g, 50.6 mmol) in POCl₃ (13.7 ml, 147 mmol) was added triethylamine (7.05 ml, 50.6 mmol) at 0 °C slowly over 30 min. After addition, the ice bath was removed and was stirred at 80 °C for 1 h. The reaction mixture was cooled to rt and slowly quenched by adding it to crushed ice. The resulting slurry was diluted with DCM (250 mL) and slowly neutralized with 2M Na₂CO₃ solution. Once neutralized the layers were separated and the organic layer was dried (Na₂SO₄), filtered and concentrated to give 3,5-dibromo-4-chloro-2-methylpyridine (14 g, 49 mmol, 97 % yield) as a off white solid. LCMS Method 4: retention time = 1.47 min.; observed ion = 285.7. ¹H NMR (500 MHz, CHLOROFORM-d) δ 8.56 (s, 1H), 2.72 (s, 3H).



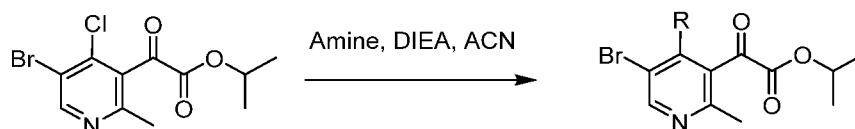
To a 25 mL RB flask equipped with a stir bar and placed under N₂ was added THF (9 ml) and 3,5-dibromo-4-chloro-2-methylpyridine (1.0 g, 3.5 mmol). The mixture was warmed to 60 °C. To the solution was added isopropylmagnesium chloride (2 M solution in THF) (1.8 ml, 3.7 mmol) dropwise at 60 °C. The solution was stirred for 1 minute. Then, to the solution was added bis(methylthio)copper(III) bromide (83 mg, 0.350 mmol) (copper bromide dimethylsulfide complex) as a solid at once. The solution was stirred at rt for 5 min. Then, to a dry 50 mL rb flask equipped with a stir bar and placed under N₂ atm was added THF (9 ml) and isopropyl 2-chloro-2-oxoacetate (580 mg, 3.85 mmol). The flask was placed in a -78 °C bath and was stirred for 10 min. To the flask was added the organometallic suspension/solution prepared above via addition funnel. The mixture remained a suspension of fine black precipitate and a pale orange solution. The bath was allowed to warm to rt with stirring. LCMS analysis after 1.5h found a peak with the expected product mass. Then, to the reaction mixture was added diethanolamine (403 µl, 4.21 mmol, (the diethanolamine is expected to coordinate both the Cu and the Mg) The mixture was transferred to a separatory funnel using water and Et₂O. The mixture was diluted with water and was extracted with Et₂O. The combined organics were washed with brine; dried over Na₂SO₄ and filtered. The solution was concentrated in vacuo. The resulting residue was dissolved in a minimal of acetone and then concentrated onto celite in

vacuo. The resulting powder was subjected to SiO₂ purification. (Biotage, EtOAc/hexanes gradient, 0-40% over 10 CVs). The first peak to elute is the desired minor isomer:

isopropyl 2-(5-bromo-4-chloro-2-methylpyridin-3-yl)-2-oxoacetate (186 mg, 0.580 mmol, 16.56 % yield). LCMS Method 4: retention time = 1.33 min.; observed ion = 320.0, 322.0.

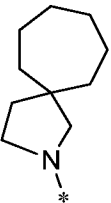
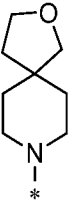
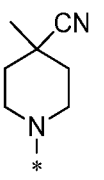
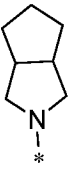
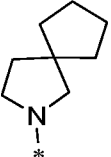
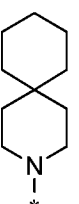
- 5 ¹H NMR (500 MHz, METHANOL-d₄) δ 8.63 (s, 1H), 4.33 (spt, *J*=6.6 Hz, 1H), 2.82 (s, 3H), 1.72 - 1.68 (m, 6H).

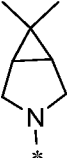
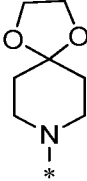
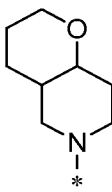
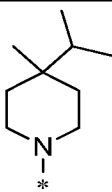
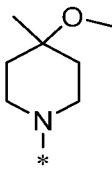
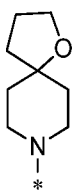
General Procedure A

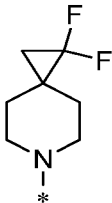
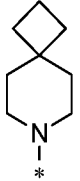
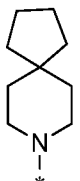
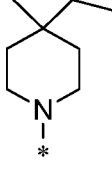
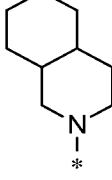
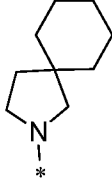


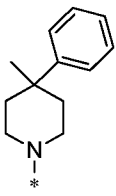
- 10 To a stirred solution of isopropyl 2-(5-bromo-4-chloro-2-methylpyridin-3-yl)-2-oxoacetate (500 mg, 1.56 mmol) and N-ethyl-N-isopropylpropan-2-amine (817 μl, 4.68 mmol, 3 equiv) in dry acetonitrile (0.2 M) was added the appropriate amine (1 equiv) and the resulting solution was placed in a heating block pre-heated to 80°C and stirred for 2 days. The reaction was then concentrated, adsorbed onto celite and was purified on silica
- 15 gel (Biotage, EtOAc/hexanes gradient, 0-50% over 10 CVs) to give the expected product consistent by LCMS.

R	Product name	LCMS Method	LCMS retention time (min)	Observed Ion	Isolated Yield
	isopropyl 2-(5-bromo-2-methyl-4-(6-azaspiro[2.5]octan-6-yl)pyridin-3-yl)-2-oxoacetate	4	1.31	395.15, 397.14	73%
	isopropyl 2-(5-bromo-4-(4-fluoro-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.25	401.15, 403.15	ND

	isopropyl 2-(5-bromo-2-methyl-4-(2-azaspiro[4.6]undecan-2-yl)pyridin-3-yl)-2-oxoacetate	4	1.26	437.20, 439.20	ND
	isopropyl 2-(5-bromo-2-methyl-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-oxoacetate	4	1.14	425.15, 427.15	ND
	isopropyl 2-(5-bromo-4-(4-cyano-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.21	408.15, 410.15	ND
	isopropyl 2-(5-bromo-4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.14	395.15, 397.15	ND
	isopropyl 2-(5-bromo-2-methyl-4-(2-azaspiro[4.4]nonan-2-yl)pyridin-3-yl)-2-oxoacetate	4	1.15	409.15, 411.15	ND
	isopropyl 2-(5-bromo-2-methyl-4-(3-azaspiro[5.5]undecan-3-yl)pyridin-3-yl)-2-oxoacetate	4	1.56	437.20, 439.20	ND

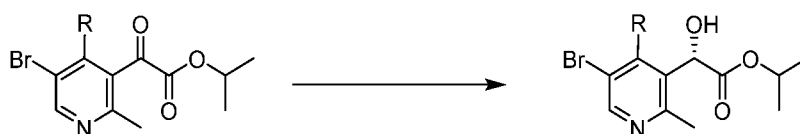
	isopropyl 2-(5-bromo-4-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.09	395.15, 397.15	59%
	isopropyl 2-(5-bromo-2-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-oxoacetate	4	1.16	427.15, 429.15	72%
	isopropyl 2-(5-bromo-4-(hexahydro-2H-pyrano[3,2-c]pyridin-6(5H)-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.17, 1.22	425.20, 427.15	80%
	isopropyl 2-(5-bromo-4-(4-isopropyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.49	425.25, 427.20	85%
	isopropyl 2-(5-bromo-4-(4-methoxy-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.17	413.15, 415.15	64%
	isopropyl 2-(5-bromo-2-methyl-4-(1-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-oxoacetate	5	1.85	427	62%

	isopropyl 2-(5-bromo-4-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-methylpyridin-3-yl)-2-oxoacetate	5	2.09	433.1	52%
	isopropyl 2-(5-bromo-2-methyl-4-(7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-oxoacetate	4	1.47	409.15, 411.15	93%
	isopropyl 2-(5-bromo-2-methyl-4-(8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-oxoacetate	5	2.36	423.2	80%
	isopropyl 2-(5-bromo-4-(4-ethyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-oxoacetate	4	1.46	411.15, 413.15	67%
	isopropyl 2-(5-bromo-2-methyl-4-((4aR,8aR)-octahydroisoquinolin-2(1H)-yl)pyridin-3-yl)-2-oxoacetate	4	1.49	423.20, 425.20	88%
	isopropyl 2-(5-bromo-2-methyl-4-(2-azaspiro[4.5]decan-2-yl)pyridin-3-yl)-2-oxoacetate	5	2.33	425.2	68%

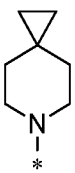
	isopropyl 2-(5-bromo-2-methyl-4-(4-methyl-4-phenylpiperidin-1-yl)pyridin-3-yl)-2-oxoacetate	4	1.44	459.20, 461.20	77%
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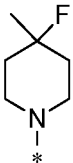
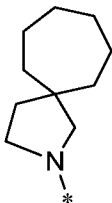
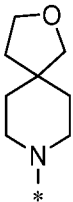
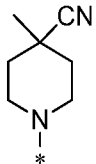
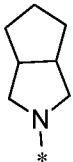
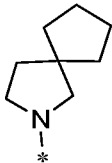
* ND = yield not determined. The product was carried directly into the next step

General Procedure B



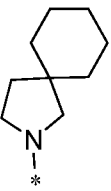
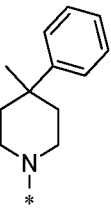
- 5 To a stirred solution of the starting material (1.2 mmol) and (R)-1-methyl-3,3-diphenyltetrahydro-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole (1M in toluene) (0.180 ml, 0.180 mmol, .15 equiv) in toluene (6 ml, 0.2M) was added dropwise catecholborane (50% in toluene, 0.360 ml, 1.680 mmol, 1.4 equiv) at -40 °C. Then the reaction (which were solutions) were placed in a -20°C freezer overnight. Each reaction was then, diluted with
- 10 EtOAc and sat Na₂CO₃. The mixture was vigorously stirred for 1 hr. The aq. layer separated and organicc layer washed with sat Na₂CO₃ 2x, dried (Na₂SO₄), filtered, concentrated and purified on silica by flash chromatography (EtOAc/Hex gradient 0-100% over 10 CVs) to afford the expected product consistent by LCMS.

R	Product name	LCMS Method	LCMS retention time (min)	Observed Ion	Isolated Yield
	isopropyl (S)-2-(5-bromo-2-methyl-4-(6-azaspiro[2.5]octan-6-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.11	397.20, 399.15	86%

	isopropyl (S)-2-(5-bromo-4-(4-fluoro-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.04	403.20, 405.15	72%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.6]undecan-2-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.22	439.25, 441.25	82%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-hydroxyacetate	4	0.974	427.20, 429.20	57%
	isopropyl (S)-2-(5-bromo-4-(4-cyano-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.13	410.20, 412.15	35%
	isopropyl (2S)-2-(5-bromo-4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.13	397.20, 399.15	48%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.4]nonan-2-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.11	411.10, 413.15	71%

	isopropyl (S)-2-(5-bromo-2-methyl-4-(3-azaspiro[5.5]undecan-3-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.13	439.25, 441.25	95%
	isopropyl (2S)-2-(5-bromo-4-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.09	397.15, 399.15	76%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.01	429.15, 431.20	71%
	isopropyl (2S)-2-(5-bromo-4-(hexahydro-2H-pyrano[3,2-c]pyridin-6(5H)-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.08	427.25, 429.25	84%
	isopropyl (S)-2-(5-bromo-4-(4-isopropyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.35	427.30, 429.25	83%
	isopropyl (S)-2-(5-bromo-4-(4-methoxy-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.26	415.20, 417.20	78%

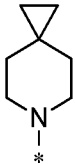
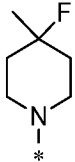
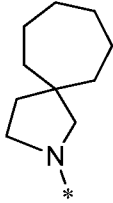
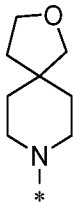
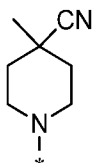
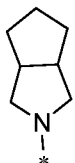
	isopropyl (S)-2-(5-bromo-2-methyl-4-(1-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-hydroxyacetate	4	0.967	427.15, 429.15	97%
	isopropyl (S)-2-(5-bromo-4-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.11	433.15, 435.15	77%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.21	411.15, 413.15	98%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.26	425.15, 427.20	89%
	isopropyl (S)-2-(5-bromo-4-(4-ethyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-hydroxyacetate	4	1.21	413.20, 415.20	97%
	isopropyl (S)-2-(5-bromo-2-methyl-4-((4aR,8aR)-octahydroisoquinolin-2(1H)-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.26	423.20, 425.25	84%

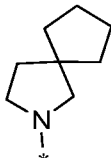
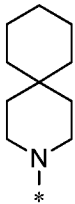
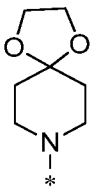
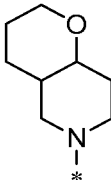
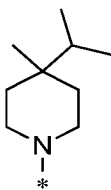
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.5]decan-2-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.16	425.20, 427.15	91%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(4-methyl-4-phenylpiperidin-1-yl)pyridin-3-yl)-2-hydroxyacetate	4	1.25	459.20, 461.25	81%

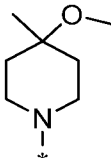
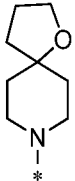
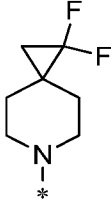
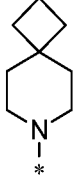
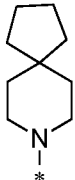
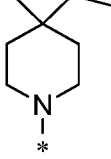
General Procedure C

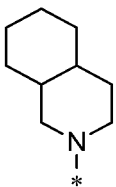
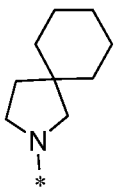
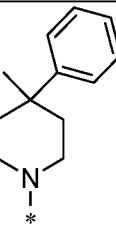


Perchloric acid (70%, 1.1 equiv) was added at once to a solution of the appropriate
 5 chiral alcohol starting material (1 equiv) in a r.b. flask with septum equipped with a
 balloon. Then 2-methylprop-1-ene (g) was bubbled into the mixture until the balloon began
 to inflate and then the gas was turned off. The reaction was allowed to stir overnight. The
 reaction mixture was diluted with more DCM and then washed with sat. Na₂CO₃ (2x) to
 make the pH basic. Then the organic phase was washed with brine and dried over Na₂SO₄,
 10 filtered and concentrated. The residue was adsorbed onto celite and was purified on silica
 gel (Biotage, EtOAc/hexanes gradient, 0-100% over 10 CVs) to afford the desired product
 consistent by LCMS.

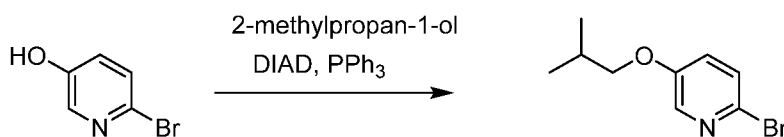
R	Product	LCMS Method	LCMS retention time (min)	Observed Ion	Isolated Yield
	isopropyl (S)-2-(5-bromo-2-methyl-4-(6-azaspiro[2.5]octan-6-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.41	453.25, 455.25	41%
	isopropyl (S)-2-(5-bromo-4-(4-fluoro-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.32	459.25, 461.25	16%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.6]undecan-2-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.55	495.35, 497.35	11%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.22	483.35, 485.30	48%
	isopropyl (S)-2-(5-bromo-4-(4-cyano-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.26	466.25, 468.25	58%
	isopropyl (2S)-2-(5-bromo-4-(hexahydrocyclopenta[c]pyrrol-2(1H)-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.39	453.25, 455.25	65%

	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.4]nonan-2-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.42	467.30, 469.30	54%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(3-azaspiro[5.5]undecan-3-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.62	495.30, 497.35	48%
	isopropyl (2S)-2-(5-bromo-4-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.46	453.25, 455.25	32%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.22	485.30, 487.25	55%
	isopropyl (2S)-2-(5-bromo-4-(hexahydro-2H-pyrano[3,2-c]pyridin-6(5H)-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.36	483.40, 485.40	25%
	isopropyl (S)-2-(5-bromo-4-(4-isopropyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.65	483.40, 485.40	48%

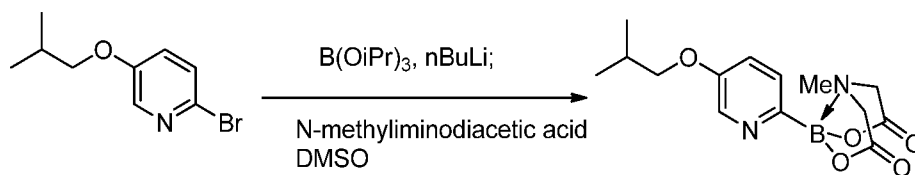
	isopropyl (S)-2-(5-bromo-4-(4-methoxy-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.27	471.25, 473.25	74%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(1-oxa-8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.21	483.35, 485.35	80%
	isopropyl (S)-2-(5-bromo-4-(1,1-difluoro-6-azaspiro[2.5]octan-6-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.38	489.30, 491.30	73%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.53	467.25, 469.25	57%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(8-azaspiro[4.5]decan-8-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.56	481.3, 483.35	79%
	isopropyl (S)-2-(5-bromo-4-(4-ethyl-4-methylpiperidin-1-yl)-2-methylpyridin-3-yl)-2-(tert-butoxy)acetate	4	1.52	469.30, 471.30	71%

	isopropyl (S)-2-(5-bromo-2-methyl-4-((4aR,8aR)-octahydroisoquinolin-2(1H)-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.56	481.30, 483.30	ND
	isopropyl (S)-2-(5-bromo-2-methyl-4-(2-azaspiro[4.5]decan-2-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.47	481.35, 483.30	78%
	isopropyl (S)-2-(5-bromo-2-methyl-4-(4-methyl-4-phenylpiperidin-1-yl)pyridin-3-yl)-2-(tert-butoxy)acetate	4	1.5	517.30, 519.35	ND

* ND = yield not determined. The product was carried directly into the next step



To a 500 mL r.b. flask equipped with a large stir bar was added 6-bromopyridin-3-ol (10.0 g, 57.5 mmol), 2-methylpropan-1-ol (4.26 g, 57.5 mmol), triphenylphosphine (15.8 g, 60.3 mmol) and THF (192 mL). To the stirring solution was added DIAD (11.73 mL, 60.3 mmol) and after 15 min the reaction solution was concentrated in vacuo. To the crude reaction product was added hexanes:Et₂O (1:1, 250 mL) and stirred. A significant amount of crystalline material (Ph₃PO) precipitated was removed via filtration. The filtrate was concentrated in vacuo and the residue was dissolved in a minimal of acetone and concentrated onto Celite. The resulting powder was subjected to SiO₂ purification on the Biotage (120 g column) 0-100% 10 CVs to afford 2-bromo-5-isobutoxypyridine (12.7 g, 96%) as a clear oil. LCMS Method 4: retention time = 1.36 min.; observed ion = 230.0, 232.0. ¹H NMR (500 MHz, CHLOROFORM-d) δ 8.07 (d, *J*=3.0 Hz, 1H), 7.44 - 7.25 (m, 1H), 7.11 (dd, *J*=8.8, 3.2 Hz, 1H), 3.76 (d, *J*=6.5 Hz, 2H), 2.17 - 2.06 (m, 1H), 1.05 (d, *J*=6.8 Hz, 6H).



To a dry 250 mL r.b.flask equipped with a large stir bar was added 2-bromo-5-isobutoxypyridine (12.7 g, 55.2 mmol). The flask was placed under N₂ atm (vac/fill x 3), then to the flask was added THF (97 ml) and triisopropyl borate (12.9 ml, 55.7 mmol). The solution was degassed with N₂ 2x and cooled in a -78 °C bath. To the solution was added dropwise n-butyllithium in hexanes (22.3 ml, 55.7 mmol) at a rate necessary to avoid build-up of any localized dark discoloration (usually visible in the central vortex with fast stirring). The rate was approximately 0.25-0.50 mL/min. At the completion of the addition, the solution slowly began to turn dark yellow. Stirring was maintained for 20 min upon which the solution was observed to be a light amber. The bath was removed and the solution was allowed to warm to r.t. with stirring. As the solution warmed, the color deepened even more significantly. After 3 h the reaction solution was carried forward into the distillation step.

The distillation setup:

A 3-neck 250 mL flask equipped with a large stir bar was charged with methyliminodiacetic acid (16.24 g, 110 mmol) and DMSO (97 ml). The center neck was fitted with a pressure-equalizing addition funnel vented to positive N₂ pressure. Another neck was fitted with a rubber septum through which a thermocouple was inserted to monitor internal temperature. The final neck was fitted with a short-path distillation apparatus collecting in a 100 mL r.b. flask and vented to a bubbler. This provides a slow stream of N₂ carrier gas through the setup and out through the bubbler so that THF vapor does not accumulate.

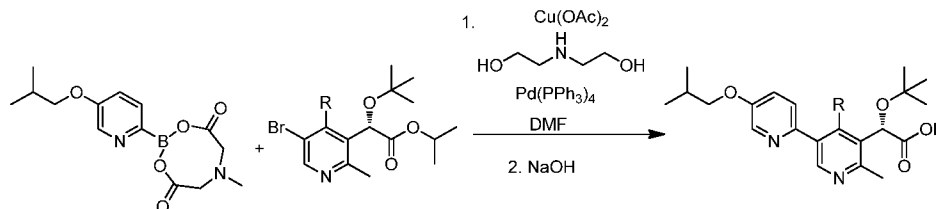
Distillation:

The reaction solution containing the boronate was transferred to the addition funnel. The 3-neck flask was heated with an oil bath (160 °C). Once the internal temperature had reached 115-120 °C the boronate solution was added dropwise at a rate necessary to maintain an internal temp of 115-120 °C. The addition took approximately 20 min. The

receiver flask containing the THF was exchanged for an empty 100 mL r.b. flask. The bubbler line connected to the vacuum arm of the distillation apparatus was exchanged for a tube running to the rotovap. The N₂ source was closed. The system was placed under vacuum, slowly ramping upon at which the DMSO distilled. The distillation was

maintained until only trace DMSO remained. The residue was dissolved in MeCN upon which only the MIDA (white powder) did not dissolve. The mixture was concentrated onto celite in vacuo. The resulting powder was subjected to SiO₂ purification on the Biotage (0-100% EtOAc/ACN gradient over 10 CVs). TLC was performed with 1:1 EA/ACN looking at it with both UV and then KMnO₄ staining (to observe biproduct). The fractions containing the product were collected and concentrated to afford the desired product 2-(5-isobutoxypyridin-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (7.3 g, 23.85 mmol, 43.2 % yield) as a white solid. LCMS Method 5: retention time = 1.35 min.; observed ion = 307.2. ¹H NMR (500 MHz, Acetone) δ 8.45 - 8.38 (m, 1H), 7.60 - 7.54 (m, 1H), 7.29 (dd, *J*=8.4, 2.9 Hz, 1H), 4.34 (d, *J*=16.6 Hz, 2H), 4.17 (d, *J*=16.6 Hz, 2H), 3.90 - 3.84 (m, 2H), 2.78 (s, 3H), 2.15 - 2.09 (m, 1H), 1.05 (d, *J*=6.8 Hz, 6H).

General Procedure D



To a 5 mL microwave vial equipped with a stir bar was added tripotassium phosphate (0.480 mmol), Pd(Ph₃P)₄ (0.019 mmol), 2-(5-isobutoxypyridin-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione compound contaminated with 2-butyl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (0.144 mmol), the appropriate 5-bromopyridine core (0.096 mmol), diacetoxycopper (0.048 mmol) and diethanolamine (0.096 mmol). The vial was sealed and degassed with N₂ (vac/fill x 3). Then to the vial was added DMF (1 ml) and was placed in a 100 °C heating block and stirred for 16 hr (overnight). The reaction was purified on silica gel (Biotage, 24g column, EtOAc/hexanes gradient, 0-100% over 10 CVs) to give the ester intermediate. This material was taken up in ethanol (2 mL) and treated with sodium hydroxide (0.100 ml, 0.500 mmol, 5 N aq) in a 2 dram pressure relief vial at rt. The reaction was then placed in 100 °C heating block and allowed to stir until

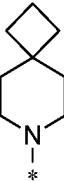
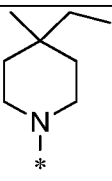
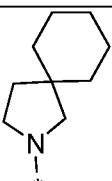
hydrolysis was complete as deemed by LCMS (3 hr). The sample was then purified prep-HPLC to afford the corresponding carboxylic acid.

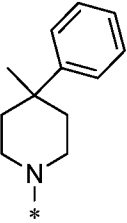
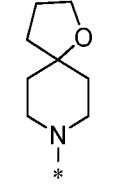
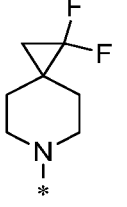
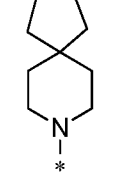
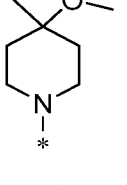
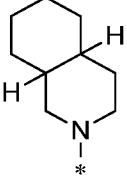
In some cases, pairs of diastereomers were isolated but which was which was not determined and so the flat structure is shown twice, for example, Examples **9** and **10**.

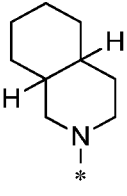
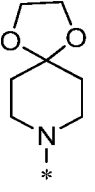
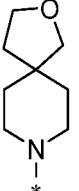
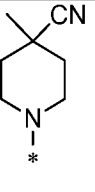
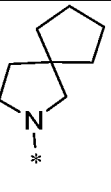
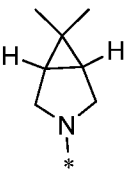
5

General Procedure D was used for Examples **1** - **23**

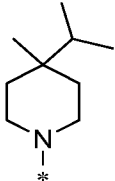
Representative ¹H NMR; Example **1**: ¹H NMR (500 MHz, DMSO-d₆) δ 8.33 (br s, 1H), 8.11 (s, 1H), 7.48 (br d, *J*=8.5 Hz, 1H), 7.40 (d, *J*=8.5 Hz, 1H), 5.86 (br s, 1H), 3.92 - 3.82 (m, 2H), 2.56 - 2.53 (m, 2H), 2.49 - 2.45 (m, 3H), 2.05 (dt, *J*=13.3, 6.5 Hz, 2H), 1.78 (br s, 2H), 1.66 (br s, 4H), 1.45 (br s, 3H), 1.38 (br s, 1H), 1.23 (s, 1H), 1.11 (s, 9H), 1.00 (br d, *J*=6.4 Hz, 6H)

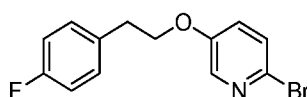
R Example	Name	% Yield	LCMS Method	RT (min)	Obs. MS Ion
 1	(2S)-2-(4'-{7-azaspiro[3.5]nonan-7-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	17.2	1	2.02	496.3
 2	(2S)-2-(tert-butoxy)-2-[4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid	40.7	2	2.07	498.3
 3	(2S)-2-(4'-{2-azaspiro[4.5]decan-2-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	21.2	2	2.05	510.3

 4	(2S)-2-(tert-butoxy)-2-[6'-methyl-4'-(4-methyl-4-phenylpiperidin-1-yl)-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid	62.7	2	2.08	546.3
 5	(2S)-2-(tert-butoxy)-2-[6'-methyl-5-(2-methylpropoxy)-4'-{1-oxa-8-azaspiro[4.5]decan-8-yl}-[2,3'-bipyridine]-5'-yl]acetic acid	61.8	2	1.61	512.3
 6	(2S)-2-(tert-butoxy)-2-(4'-{1,1-difluoro-6-azaspiro[2.5]octan-6-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)acetic acid	109.7	2	1.79	518.2
 7	(2S)-2-(4'-{8-azaspiro[4.5]decan-8-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	54.2	1	2.03	510.3
 8	(2S)-2-(tert-butoxy)-2-[4'-(4-methoxy-4-methylpiperidin-1-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid	59.5	1	1.58	500.3
 9	(2S)-2-(tert-butoxy)-2-[4'-(decahydroisoquinolin-2-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid (first eluting isomer)	21.5	2	2.12	510.3

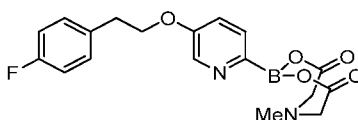
 10	(2S)-2-(tert-butoxy)-2-[4'-(decahydroisoquinolin-2-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid (second eluting isomer)	20.8	1	2.06	510.3
 11	(2S)-2-(tert-butoxy)-2-(4'-(1,4-dioxo-8-azaspiro[4.5]decan-8-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)acetic acid	41.2	2	1.59	514.3
 12	(2S)-2-(tert-butoxy)-2-[6'-methyl-5-(2-methylpropoxy)-4'-(2-oxa-8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridine]-5'-yl]acetic acid	72.1	1	1.52	512.3
 13	(2S)-2-(tert-butoxy)-2-[4'-(4-cyano-4-methylpiperidin-1-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid	52	2	1.65	495.3
 14	(2S)-2-(4'-(2-azaspiro[4.4]nonan-2-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	64.7	1	1.81	496.3
 15	(2S)-2-(tert-butoxy)-2-(4'-(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-3-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)acetic acid	39.5	1	1.72	482.3

 16	(2S)-2-(4'-{3-azaspiro[5.5]undecan-3-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	33.7	2	2.21	524.3
 17	(2S)-2-(tert-butoxy)-2-[6'-methyl-5-(2-methylpropoxy)-4'-{octahydrocyclopenta[c]pyrrol-2-yl}-[2,3'-bipyridine]-5'-yl]acetic acid	50.2	1	1.77	482.3
 18	(2S)-2-(4'-{6-azaspiro[2.5]octan-6-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	23.1	2	1.97	482.2
 19	(2S)-2-(4'-{2-azaspiro[4.6]undecan-2-yl}-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	64.6	1	2	524.3
 20	(2S)-2-(tert-butoxy)-2-[4'-(4-fluoro-4-methylpiperidin-1-yl)-6'-methyl-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl]acetic acid	36.7	2	1.78	488.2
 21	(2S)-2-(tert-butoxy)-2-[6'-methyl-5-(2-methylpropoxy)-4'-{octahydro-2H-pyrano[3,2-c]pyridin-6-yl}-[2,3'-bipyridine]-5'-yl]acetic acid (first eluting isomer)	15.3	2	1.7	512.3
 22	(2S)-2-(tert-butoxy)-2-[6'-methyl-5-(2-methylpropoxy)-4'-{octahydro-2H-pyrano[3,2-c]pyridin-6-yl}-[2,3'-	18.8	1	1.59	512.3

22	bipyridine]-5'-yl]acetic acid (second eluting isomer)				
 23	(2S)-2-(tert-butoxy)-2-{6'-methyl-4'-[4-methyl-4-(propan-2-yl)piperidin-1-yl]-5-(2-methylpropoxy)-[2,3'-bipyridine]-5'-yl}acetic acid	54.8	2	2.15	512.2

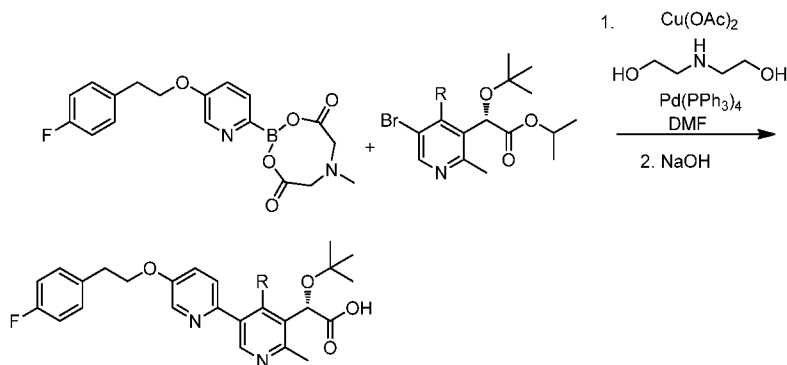


To a 40 mL vial equipped with a stir bar was added 1-(2-bromoethyl)-4-fluorobenzene (2.334 g, 11.49 mmol) and 6-bromopyridin-3-ol (1.00 g, 5.75 mmol), then DMSO (30 mL) and potassium carbonate (1.589 g, 11.49 mmol). The vial was vented to a N₂ stream (bubbler), then placed in a 50 °C oil bath with stirring for 18h. (t=0). To the reaction solution was added 1-(2-bromoethyl)-4-fluorobenzene (2.334 g, 11.49 mmol). The mixture was stirred at 50 °C for 3h. To the reaction mixture was added potassium carbonate (1.589 g, 11.49 mmol). The reaction mixture was stirred for 18h. The reaction mixture was cooled to r.t., then was transferred to a 500 mL separatory funnel and was diluted with water (150 mL). The mixture was extracted with Et₂O (100 mL). The organic phase was washed with brine (50 mL), then dried over MgSO₄, filtered, then concentrated in vacuo. The resulting residue was dissolved in a min. of acetone and then was concentrated onto Celite in vacuo. The resulting powder was subjected to SiO₂ purification (80g SiO₂, hexanes:EtOAc 100:0→80:20) to afford a colorless oil that crystallized upon standing to afford 2-bromo-5-(4-fluorophenoxy)pyridine (1.5337 g, 90 %) as a colorless, crystalline solid. ¹H NMR (500MHz, CDCl₃) δ 8.04 (d, *J*=3.0 Hz, 1H), 7.36 (dd, *J*=8.7, 0.5 Hz, 1H), 7.26 - 7.21 (m, 2H), 7.08 (dd, *J*=8.8, 3.2 Hz, 1H), 7.05 - 6.99 (m, 2H), 4.18 (t, *J*=6.8 Hz, 2H), 3.08 (t, *J*=6.8 Hz, 2H).



To a dry 50 mL Schlenk flask equipped with a large stir bar was added 2-bromo-5-(4-fluorophenoxy)pyridine (6.103 g, 20.61 mmol). The flask was placed under nitrogen

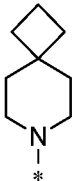
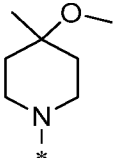
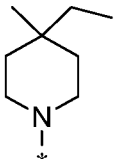
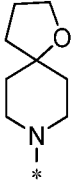
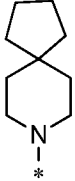
atmosphere. To the flask was added THF (36 ml) and triisopropyl borate (4.83 ml, 20.8 mmol). The flask was sealed with a septum, then the solution was sparged with N₂ for 5 minutes. The flask was cooled in a -78 °C bath. To the solution was added dropwise n-butyllithium in hexanes (8.33 ml, 20.8 mmol) at a rate necessary to avoid build-up of any localized dark discoloration. The rate was approximately 0.25-0.50 mL/min. At the completion of the addition the solution slowly began to turn a deep amber color. The mixture was stirred for 1h up which the solution was observed to be a deep amber color. The bath was removed and the solution was allowed to warm to r.t. with stirring for 3h. Separately, a distillation apparatus was assembled as follows: a 3-neck 250 mL flask equipped with a large stir bar was charged with methyliminodiacetic acid (6.06 g, 41.2 mmol) and DMSO (36.2 ml); the center neck was fitted with a pressure-equalizing addition funnel vented to positive N₂ pressure; another neck was fitted with a rubber septum through which a thermocouple was inserted to monitor internal temperature; and the final neck was fitted with a short-path distillation apparatus collecting into a 250 mL r.b. flask and vented to a bubbler. The reaction solution containing the boronate was transferred to the addition funnel. The 3-neck flask was heated with an oil bath (160 °C). Once the internal temperature had reached 115-120 °C, the boronate solution was added dropwise at a rate necessary to maintain an internal temp of 115-120 °C. The addition took approximately 20 min. The receiver flask containing the THF was exchanged for an empty 200 mL r.b. flask. The bubbler line connected to the vacuum arm of the distillation apparatus was exchanged for a tube running vacuum. The N₂ source was closed. The system was placed under vacuum, slowly ramping to 30 Torr upon which the DMSO distilled. The distillation was maintained at 30 Torr until only trace DMSO remained. The resulting residue, a solid, was dissolved in MeCN upon which only a white powder did not dissolve. The mixture was concentrated onto Celite in vacuo. The resulting powder was subjected to SiO₂ purification (120g SiO₂ column, EtOAc:MeCN 100:0→0:100) on the Biotage to afford 2-(5-(4-fluorophenethoxy)pyridin-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (2.067 g, 27.0 %) as a colorless solid foam. ¹H NMR (500 MHz, acetone-d₆) δ 8.40 - 8.36 (m, 1H), 7.57 - 7.52 (m, 1H), 7.44 - 7.35 (m, 2H), 7.29 (dd, J=8.4, 2.8 Hz, 1H), 7.12 - 7.02 (m, 2H), 4.31 (d, J=16.6 Hz, 2H), 4.30 (t, J=6.7 Hz, 2H), 4.14 (d, J=16.6 Hz, 2H), 3.11 (t, J=6.7 Hz, 2H), 2.75 (s, 3H).

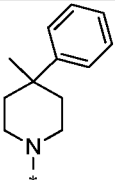
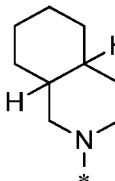
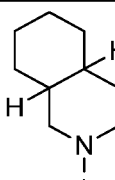
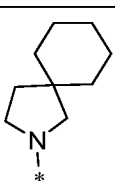
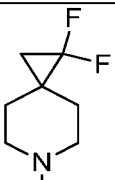
General Procedure E

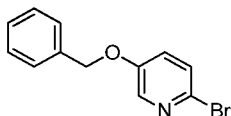
To a 5 mL microwave vial equipped with a stir bar was added tripotassium
 5 phosphate (0.480 mmol), $\text{Pd}(\text{Ph}_3\text{P})_4$ (0.019 mmol), 2-(5-(4-fluorophenethoxy)pyridin-2-yl)-
 6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (0.136 mmol), the appropriate 5-
 bromopyridine core (0.096 mmol), diacetoxycopper (8.72 mg, 0.048 mmol) and
 diethanolamine (0.096 mmol). The vial was sealed and degassed with N_2 (vac/fill x 3).
 Then to the vial was added DMF (1 ml) and was placed in a 100 °C heating block, and
 10 stirred for 16 hr overnight. The reaction was purified on silica gel (Biotage, 24g column,
 EtOAc/hexanes gradient, 0-100% over 10 CVs) to give the ester intermediate. This
 material was taken up in ethanol (2 mL) and treated with sodium hydroxide (0.100 mL,
 0.500 mmol, 5 N aq) in a 2-dram pressure relief vial at rt. The reaction was then placed in
 100 °C heating block and allowed to stir until hydrolysis was complete as deemed by
 15 LCMS (3 hr). The sample was then purified by prep-HPLC to afford the corresponding
 carboxylic acid.

General Procedure E was used for Examples **24 - 33**

20 Representative ^1H NMR; Example **24**: ^1H NMR (500 MHz, METHANOL-d_4) δ 8.32 (d,
 $J=2.7$ Hz, 1H), 8.15 (s, 1H), 7.52 (dd, $J=8.7, 2.9$ Hz, 1H), 7.42 - 7.35 (m, 3H), 7.08 - 7.03
 (m, 2H), 5.83 (s, 1H), 4.35 (t, $J=6.3$ Hz, 2H), 3.15 (t, $J=6.6$ Hz, 2H), 2.74 (br s, 2H), 2.65
 (s, 3H), 1.92 - 1.85 (m, 2H), 1.78 - 1.62 (m, 10H), 1.19 (s, 9H)

R Example	Name	% Yield	LCMS Method	RT (min)	Obs. MS Ion
 24	(2S)-2-(4'-{7-azaspiro[3.5]nonan-7-yl}-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	25.6	1	2.11	562.3
 25	(2S)-2-(tert-butoxy)-2-{5-[2-(4-fluorophenyl)ethoxy]-4'-(4-methoxy-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridine]-5'-yl}acetic acid	53.8	1	1.77	566.3
 26	(2S)-2-(tert-butoxy)-2-[4'-(4-ethyl-4-methylpiperidin-1-yl)-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl]acetic acid	28.5	2	2.01	564.4
 27	(2S)-2-(tert-butoxy)-2-{5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-4'-{1-oxa-8-azaspiro[4.5]decan-8-yl}-[2,3'-bipyridine]-5'-yl}acetic acid	50.3	1	1.68	578.2
 28	(2S)-2-(4'-{8-azaspiro[4.5]decan-8-yl}-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	31	2	2.04	576.3

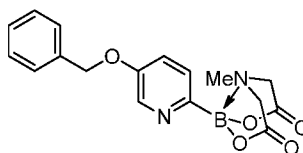
 29	(2S)-2-(tert-butoxy)-2-{5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-4'-(4-methyl-4-phenylpiperidin-1-yl)-[2,3'-bipyridine]-5'-yl}acetic acid	39.7	1	2.11	612.2
 30	(2S)-2-(tert-butoxy)-2-[4'-(decahydroisoquinolin-2-yl)-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl]acetic acid (first eluting isomer)	21.8	1	2.14	576.3
 31	(2S)-2-(tert-butoxy)-2-[4'-(decahydroisoquinolin-2-yl)-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl]acetic acid (second eluting isomer)	15.4	1	2.15	576.3
 32	(2S)-2-(4'-{2-azaspiro[4.5]decan-2-yl}-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl)-2-(tert-butoxy)acetic acid	34.7	2	1.95	576.3
 33	(2S)-2-(tert-butoxy)-2-(4'-{1,1-difluoro-6-azaspiro[2.5]octan-6-yl}-5-[2-(4-fluorophenyl)ethoxy]-6'-methyl-[2,3'-bipyridine]-5'-yl)acetic acid	18.6	2	1.8	584.2



To a 1L round bottom flask equipped with a large stir bar was added 6-bromopyridin-3-ol (24.69 g, 142 mmol), benzyl alcohol (15.42 mL, 149 mmol),
5 triphenylphosphine (39.1 g, 149 mmol) and THF (600 mL). The flask was placed in a r.t. water bath. To the stirred solution was added in six portions DIAD (29.0 mL, 149 mmol).

The internal temperature increased from 20 deg to 35 deg C, and was 35 deg C at the completion of the addition. After stirring for 18 h the reaction solution was concentrated in vacuo to afford a liquid residue. The material was diluted with hexane:Et₂O (1:1, 850 mL). A precipitate was immediately formed. The mixture was stirred for 5 minutes, then the liquid was decanted and reserved. The solids were treated with Et₂O (200 mL), and the mixture was stirred for 5 minutes. The solution was diluted with hexanes (200 mL), and the mixture was then stirred for 5 minutes. The mixture and the reserved solution were combined and filtered through a fine-fritted vacuum funnel. The filtrate was concentrated in vacuo. The resulting residue was diluted with a small amount of acetone and then concentrated onto Celite in vacuo. The resulting powder was subjected to SiO₂ chromatography (330g SiO₂ column, hexanes:EtOAc 100:0 → 80:20) to afford 5-(benzyloxy)-2-bromopyridine as a colorless, crystalline solid (24.84 g, 66%). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.16 (d, *J*=3.2 Hz, 1H), 7.45 - 7.36 (m, 6H), 7.18 (dd, *J*=8.6, 3.2 Hz, 1H), 5.12 (s, 2H).

Alternative procedure: To a stirred solution of 6-bromopyridin-3-ol (100 g, 575 mmol), K₂CO₃ (119 g, 862 mmol) in acetone (1 L) was added benzyl bromide (0.075 L, 632 mmol). The mixture was stirred for 3 h at 80 °C. LCMS showed completion of reaction. Then, the mixture was cooled to 20 °C and poured into water (250 mL). The precipitate was filtered, taken up in DCM and washed with sat. NaHCO₃ (50 mL), water (50 mL), brine (50 mL) and concentrated to afford 5-(benzyloxy)-2-bromopyridine (120 g, 454 mmol, 79 % yield) as a off-white solid.



To a dry 250 mL round bottom flask equipped with a large stir bar and charged with 5-(benzyloxy)-2-bromopyridine (21.8527 g, 83 mmol) was added THF (150 ml) and triisopropyl borate (19.40 ml, 84 mmol). The flask was sealed with a rubber septum, then the solution was sparged with N₂ for 5 min. The flask was cooled in a -78 °C bath. To the solution was added dropwise over 30 min n-butyllithium in hexanes (33.4 ml, 84 mmol). The cold bath was removed and the solution was allowed to slowly warm to r.t. with stirring. After 2 h the solution was transferred to a pressure-equalizing addition funnel. The addition funnel was fitted onto the center neck of a 3-neck 250 mL flask equipped with a large stir bar was charged with N-methyliminodiacetic acid (24.35 g, 165 mmol) and

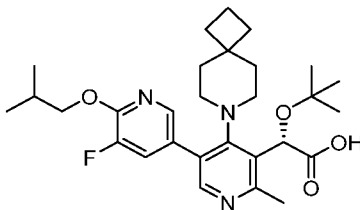
DMSO (150 ml). A side neck was fitted with a thermocouple. The other side neck was fitted with a water-cooled short-path distillation apparatus collecting into a 250 mL round bottom flask and vented to a bubbler. The addition funnel was capped with a gas adapter connected to a low-volume stream of N₂ gas. The 3-neck flask was heated with an oil bath (150 °C). Once the DMSO solution had reached 115-120 °C the boronate solution was added dropwise at a rate necessary to maintain an internal temp of 115-120 °C. The blue boronate solution immediately becomes a red/amber color upon contacting the DMSO solution. The reaction mixture is a deep amber solution. Upon completion of the addition the receiver flask containing THF was exchanged for an empty 200 mL round bottom flask. The bubbler line connected to the vacuum arm of the distillation apparatus was exchanged for a controlled vacuum source. The N₂ source feeding into the addition funnel was closed. The system was placed under vacuum, slowly ramping to 30 Torr. The receiver flask was emptied, then the vacuum was slowly ramped to 2 Torr. The bath temperature was set to 125 °C and the pressure was maintained at 2 Torr. When the majority of DMSO had been removed the flask was opened to ambient atmosphere. To the flask was added MeCN (100 mL). Heating was maintained until the solvent had reached reflux, then heating was stopped. To the hot mixture was added Celite. The mixture was concentrated in vacuo to afford a clumpy solid which was subjected to SiO₂ chromatography (EtOAc:MeCN 100:0 → 0:100) to afford the desired product as a colorless solid. This material was dissolved/suspended in MeCN (100 mL), then was diluted with Et₂O (400 mL). The crystalline solid was collected via vacuum filtration. The solids were dried under high vacuum to afford (5-(benzyloxy)pyridin-2-yl)boronic acid MIDA ester as a colorless, fine crystalline solid (5.81 g, 21%). ¹H NMR (500 MHz, ACETONITRILE-d₃) δ 8.50 - 8.42 (m, 1H), 7.56 (d, *J*=8.4 Hz, 1H), 7.49 - 7.44 (m, 2H), 7.44 - 7.38 (m, 2H), 7.38 - 7.33 (m, 1H), 7.31 (dd, *J*=8.4, 2.9 Hz, 1H), 5.16 (s, 2H), 4.10 - 4.04 (m, 2H), 3.98 - 3.92 (m, 2H), 2.54 (s, 3H).

Simplified procedure: To a solution of 5-(benzyloxy)-2-bromopyridine (98 g, 371 mmol) and triisopropyl borate (77 g, 408 mmol) in THF (800mL) was added n-butyllithium (193 mL, 482 mmol) at -78 °C and stirred for 20 min at -78°C. Then, the reaction mixture was stirred at rt for 3 h. The reaction mixture was added to a solution of 2,2'-(2,2'-(methylazanediyl)diacetic acid (109 g, 742 mmol) in DMSO (800 mL) at 115-120 °C (internal temperature). Then, the THF and DMSO was distilled off over 2 h to remove as much solvent as possible. The reaction flask was cooled, diluted with 3000 mL

of ethyl acetate and washed with water (2000 mL x2), dried and concentrated. The residue was purified by silica gel chromatography to give 2-(5-(benzyloxy)pyridin-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (41 g, 120 mmol, 32.2 % yield) as pale solid.

5

Example 34

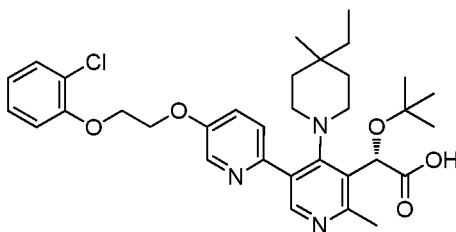


(S)-2-(tert-Butoxy)-2-(5'-fluoro-6'-isobutoxy-6-methyl-4-(7-azaspiro[3.5]nonan-7-yl)-[3,3'-bipyridin]-5-yl)acetic acid

Isopropyl (S)-2-(5-bromo-2-methyl-4-(7-azaspiro[3.5]nonan-7-yl)pyridin-3-yl)-2-(tert-butoxy)acetate (45 mg, 0.096 mmol), 3-fluoro-2-isobutoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (56.8 mg, 0.193 mmol), SPhos Pd G3 (7.50 mg, 9.63 μ mol), K₃PO₄ (61.3 mg, 0.289 mmol) were combined under N₂. 1,4-Dioxane (1604 μ l) and water (321 μ l) were added under N₂. The reaction was stirred at 80 °C. for 1 hr. The reaction was concentrated, adsorbed onto celite and was purified on silica gel (Biotage, EtOAc/hexanes gradient) to afford isopropyl (S)-2-(tert-butoxy)-2-(5'-fluoro-6'-isobutoxy-6-methyl-4-(7-azaspiro[3.5]nonan-7-yl)-[3,3'-bipyridin]-5-yl)acetate. The ester was subjected to hydrolysis conditions: (1.5 mL of EtOH, 0.1 mL of 5N aq NaOH, 100°C, 3 hrs.). The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5'-fluoro-6'-isobutoxy-6-methyl-4-(7-azaspiro[3.5]nonan-7-yl)-[3,3'-bipyridin]-5-yl)acetic acid (6.5 mg). LCMS (M + H) = 514.2; Retention time (10 mM NH₄HCO₃) = 2.10.

25

Example 35



(S)-2-tert-Butoxy-2-(5-(2-(2-chlorophenoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid:

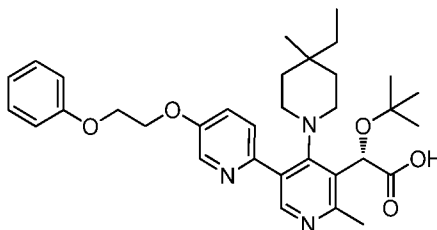
Step 1: To a solution of 2-(2-chlorophenoxy)ethan-1-ol (1.2 g, 6.95 mmol) and TEA (2.91 mL, 20.86 mmol) in THF (20 mL) was added dropwise Ms-Cl (0.813 mL, 10.43 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. LCMS showed that SM was consumed completely. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃ (10 ml) and brine (10 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated to give 2-(2-chlorophenoxy)ethyl methanesulfonate (1.1g, 4.39 mmol, 63.1 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.103 mmol) in DMF (10 mL), 2-(2-chlorophenoxy)ethyl methanesulfonate (78 mg, 0.310 mmol) and was added K₂CO₃ (71.4 mg, 0.517 mmol) and the mixture was stirred for 20 hours at 45 °C. The mixture was diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.083 mmol, 80 % yield) as a yellow oil. LCMS (M + H) = 683.1; Retention time (10 mM NH₄HCO₃) = 2.569.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.083 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (9.96 mg, 0.249 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (24.6 mg, 0.041 mmol, 49.7 % yield) as white solid. LCMS (M + H) = 596.1;

Retention time (10 mM NH_4HCO_3) = 1.604. ^1H NMR (400 MHz, MeOD) δ 8.46 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.69 (dd, J = 8.6, 3.0 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 7.9, 1.6 Hz, 1H), 7.33- 7.26 (m, 1H), 7.17 (dd, J = 8.3, 1.3 Hz, 1H), 6.97 (td, J = 7.7, 1.4 Hz, 1H), 5.81 (s, 1H), 4.59 (dd, J = 8.0, 3.8 Hz, 2H), 4.49- 4.45 (m, 2H), 3.3- 2.81 (m, 7H), 1.61- 1.26 (m, 6H), 1.21 (s, 9H), 0.84- 0.75 (m, 6H).

Example 36



(S)-2-tert-Butoxy-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-phenoxyethoxy)-2,3'-bipyridin-5'-yl)acetic acid

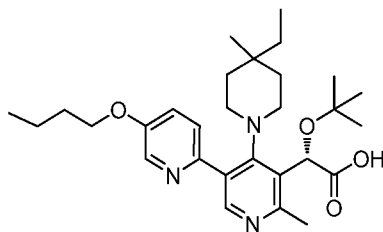
Step 1: To a solution of 2-phenoxyethan-1-ol (1 g, 7.24 mmol) and TEA (3.03 mL, 21.71 mmol) in THF (20 mL) was added dropwise Ms-Cl (0.846 mL, 10.86 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. LCMS showed that SM was consumed completely. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO_3 (10 ml) and brine (10 ml). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give 2-phenoxyethyl methanesulfonate (900 mg, 4.16 mmol, 57.5 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.103 mmol) in DMF (10 mL) was added K_2CO_3 (71.4 mg, 0.517 mmol) and 2-phenoxyethyl methanesulfonate (67.1 mg, 0.310 mmol). Then, the mixture was stirred at 45 °C for 20 hours and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na_2SO_4 , concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.057 mmol, 55.1 %

yield) as a yellow oil. LCMS (M + H) = 604.2; Retention time (10 mM NH₄HCO₃) = 2.513.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.084 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.13 mg, 0.253 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (10.9 mg, 0.019 mmol, 22.97 % yield). LCMS (M + H) = 562.2; Retention time (10 mM NH₄HCO₃) = 1.648. ¹H NMR (400 MHz, MeOD) δ 8.33 (d, *J* = 2.8 Hz, 1H), 8.06 (s, 1H), 7.53 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.23- 7.14 (m, 2H), 6.91- 6.81 (m, 3H), 5.70 (s, 1H), 4.40 (dd, *J* = 6.1, 3.0 Hz, 2H), 4.32- 4.24 (m, 2H), 3.30- 2.54 (m, 7H), 1.54 -1.17 (m, 6H), 1.09 (s, 9H), 0.75- 0.65 (m, 6H).

Example 37



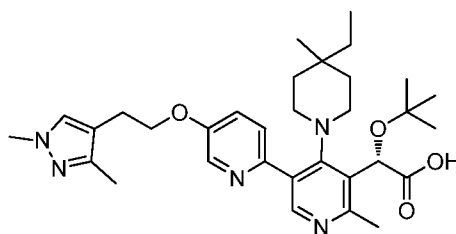
(S)-2-tert-Butoxy-2-(5-butoxy-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.103 mmol) in DMF (10 mL) was added K₂CO₃ (14.29 mg, 0.103 mmol) and 1-bromobutane (14.17 mg, 0.103 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica

gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-butoxy-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (43 mg, 0.080 mmol, 77 % yield) as a yellow oil. LCMS (M + H) = 540.2; Retention time (10 mM NH₄HCO₃) = 2.758.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-butoxy-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.096 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (11.56 mg, 0.289 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-butoxy-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (21.6 mg, 0.042 mmol, 43.9 % yield) as white solid. LCMS (M + H) = 498.1; Retention time (10 mM NH₄HCO₃) = 1.716. ¹H NMR (400 MHz, MeOD) δ 8.36 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.16 (t, J = 6.4 Hz, 2H), 2.30- 2.66 (m, 7H), 1.91- 1.77 (m, 2H), 1.64- 1.25 (m, 8H), 1.21 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H), 0.88- 0.77 (m, 6H).

Example 38



(S)-2-tert-Butoxy-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

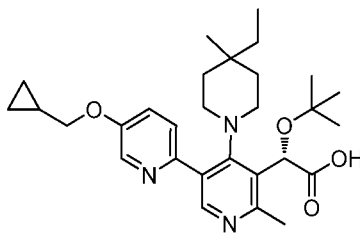
Step 1: To a solution of 2-(1,3-dimethyl-1H-pyrazol-4-yl)ethan-1-ol (250 mg, 1.783 mmol) and triethylamine (271 mg, 2.68 mmol) in DCM (10 mL) was added methanesulfonyl chloride (225 mg, 1.962 mmol) at 0 °C . The mixture was stirred at rt for 1 h. The mixture was taken up into aqueous Na₂CO₃ (20 mL) and extracted with DCM (10 ml X 3). The

combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to afford 2-(1,3-dimethyl-1H-pyrazol-4-yl)ethyl methanesulfonate (300 mg, 1.100 mmol, 61.7 % yield) as oil which was used in the next step without further purification. LCMS: retention time = 1.22 min, m/z = 219 [M+H]⁺, purity: 80% (214 nm).

5 Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.103 mmol) in DMF (10 mL) was added K₂CO₃ (71.4 mg, 0.517 mmol) and 2-(1,3-dimethyl-1H-pyrazol-4-yl)ethyl methanesulfonate (67.7 mg, 0.310 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic
10 layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (41 mg, 0.068 mmol, 65.5 % yield) as a yellow oil. LCMS (M + H)
15 = 606.2; Retention time (10 mM NH₄HCO₃) = 2.234.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (41 mg, 0.068 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.12 mg, 0.203 mmol) and stirred for 20 hours at 100 °C. The mixture was
20 concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-
25 bipyridin]-5'-yl)acetic acid (17.3 mg, 0.031 mmol, 45.3 % yield) as white solid. LCMS (M + H) = 564.2; Retention time (10 mM NH₄HCO₃) = 1.452. ¹H NMR (400 MHz, MeOD) δ 8.38 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 5.82 (s, 1H), 4.25 (t, J = 6.7 Hz, 2H), 3.80 (s, 3H), 3.23- 2.57 (m, 9H), 2.25 (s, 3H),
30 1.61-1.23 (m, 6H), 1.21 (s, 9H), 0.87- 0.74 (m, 6H).

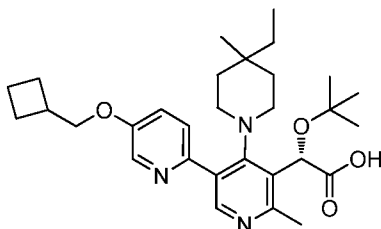
Example 39



(S)-2-tert-Butoxy-2-(5-(cyclopropylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

- 5 Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added K₂CO₃ (42.9 mg, 0.310 mmol) and (bromomethyl)cyclopropane (25.1 mg, 0.186 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over
- 10 Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.018 mmol, 29.7 % yield) as a yellow oil. LC/MS (M + H) = 538.3; Retention time (10 mM NH₄HCO₃) = 2.005.
- 15 Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.056 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.69 mg, 0.167 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated
- 20 to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (10.1 mg, 0.020
- 25 mmol, 36.5 % yield) as white solid. LCMS (M + H) = 496.2; Retention time (10 mM NH₄HCO₃) = 1.573. ¹H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.55 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 5.82 (s, 1H), 4.00 (d, J = 7.0 Hz, 2H), 3.09- 2.53 (m, 7H), 1.58-1.27 (m, 7H), 1.21 (s, 9H), 0.91- 0.76 (m, 6H), 0.73- 0.63 (m, 2H), 0.53- 0.30 (m, 2H).

Example 40



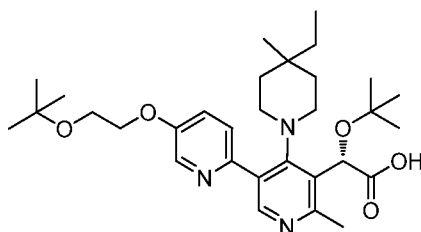
(S)-2-tert-Butoxy-2-(5-(cyclobutylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (31 mg, 0.064 mmol) in DMF (10 mL) was added K_2CO_3 (26.6 mg, 0.192 mmol) and (bromomethyl)cyclobutane (19.10 mg, 0.128 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na_2SO_4 and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (31 mg, 0.023 mmol, 35.9 % yield) as a yellow oil. LCMS (M + H) = 552.2; Retention time (10 mM NH_4HCO_3) = 2.237.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (31 mg, 0.056 mmol) in methanol (10 mL) and water (2 mL) was added NaOH (2.247 mg, 0.056 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (15.9 mg, 0.031 mmol, 55.5 % yield) as white solid. LCMS (M + H) = 510.1; Retention time (10 mM NH_4HCO_3) = 1.681. 1H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.7 Hz, 1H), 8.17 (s, 1H), 7.56 (dd, J =

ethyl-4-methylpiperidin-1-yl)-5-(2-isopropoxyethoxy)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (14.5 mg, 0.027 mmol, 60.2 % yield) as white solid. LCMS (M + H) = 528.2; Retention time (10 mM NH₄HCO₃) = 1.573. ¹H NMR (400 MHz, MeOD) δ 8.41 (d, J = 2.9 Hz, 1H), 8.17 (s, 1H), 7.60 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.28 (dd, J = 5.6, 3.2 Hz, 2H), 3.91- 3.83 (m, 2H), 3.75 (dt, J = 12.2, 6.1 Hz, 1H), 3.30-2.82 (m, 7H), 1.51-1.50 (m, 2H), 1.42-1.26 (m, 4H), 1.23 (s, 6H), 1.21 (s, 9H), 0.87- 0.79 (m, 6H).

Example 42



(S)-2-tert-Butoxy-2-(5-(2-tert-butoxyethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

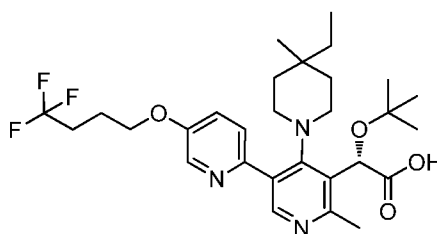
Step 1: To a solution of 2-(tert-butoxy)ethan-1-ol (1 g, 8.46 mmol) and TEA (3.54 mL, 25.4 mmol) in THF (15 mL) was added dropwise Ms-Cl (0.989 mL, 12.69 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. TLC showed that SM was consumed completely. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃, (10 ml) and brine (10 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated to give 2-(tert-butoxy)ethyl methanesulfonate (1.2g, 1.352 mmol, 15.98 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added 2-(tert-butoxy)ethyl methanesulfonate (18.26 mg, 0.093 mmol) and K₂CO₃ (17.15 mg, 0.124 mmol) and stirred for 20 hours at 45 °C. The reaction mixture was diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-4'-

(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (40 mg, 0.021 mmol, 34.6 % yield) as a yellow oil. LCMS (M + H) = 584.2; Retention time (10 mM NH₄HCO₃) = 2.714.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (40 mg, 0.069 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.22 mg, 0.206 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (14.9 mg, 0.028 mmol, 40.1 % yield) as white solid. LCMS (M + H) = 542.2; Retention time (10 mM NH₄HCO₃) = 1.623. ¹H NMR (400 MHz, MeOD) δ 8.40 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.60 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.26 (dd, J = 7.5, 4.3 Hz, 2H), 3.82 (t, J = 4.6 Hz, 2H), 3.18- 2.45 (m, 7H), 1.60- 1.24 (m, 15H), 1.21 (s, 9H), 0.87- 0.79 (m, 6H).

Example 43



(S)-2-tert-Butoxy-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(4,4,4-trifluorobutoxy)-2,3'-bipyridin-5'-yl)acetic acid

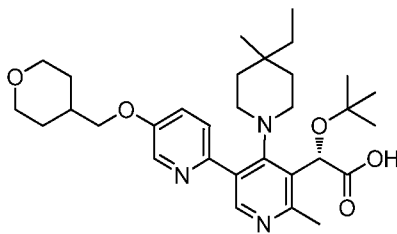
Step 1: To a solution of 4,4,4-trifluorobutan-1-ol (2 g, 15.61 mmol) and TEA (2.176 mL, 15.61 mmol) in THF (20 mL) was added dropwise Ms-Cl (1.217 mL, 15.61 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃, (10 ml) and brine (10 ml). The organic layer was dried over

Na₂SO₄, filtered and concentrated to give 4,4,4-trifluorobutyl methanesulfonate (2.5g, 11.52 mmol, 73.8 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added 4,4,4-trifluorobutyl methanesulfonate (12.79 mg, 0.062 mmol) and K₂CO₃ (8.57 mg, 0.062 mmol) and stirred for 20 hours at 45 °C. Diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (42 mg, 0.028 mmol, 44.8 % yield) as a yellow oil. LCMS (M + H) = 594.2; Retention time (10 mM NH₄HCO₃) = 2.652.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (42 mg, 0.071 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.49 mg, 0.212 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (22.9 mg, 0.042 mmol, 58.7 % yield) as white solid. LCMS (M + H) = 552.2; Retention time (10 mM NH₄HCO₃) = 1.645. ¹H NMR (400 MHz, MeOD) δ 8.41 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.59 (dd, J = 8.6, 2.9 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.24 (t, J = 6.1 Hz, 2H), 3.30- 2.66 (m, 7H), 2.45 (ddd, J = 10.9, 8.0, 5.4 Hz, 2H), 2.12 (dd, J = 10.2, 5.8 Hz, 2H), 1.75- 1.25 (m, 6H), 1.21 (s, 9H), 0.90- 0.74 (m, 6H).

Example 44



(S)-2-tert-Butoxy-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)-2,3'-bipyridin-5'-yl)acetic acid

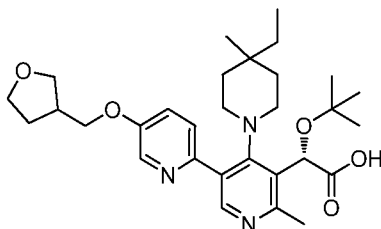
5 Step 1: To a solution of (tetrahydro-2H-pyran-4-yl)methanol (1 g, 8.61 mmol) and TEA (2.400 mL, 17.22 mmol) in THF (15 mL) was added dropwise Ms-Cl (1.006 mL, 12.91 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃ (10 ml) and brine (10 ml). The organic layer was dried over
10 Na₂SO₄, filtered and concentrated to give (tetrahydro-2H-pyran-4-yl)methyl methanesulfonate (1.1 g, 5.21 mmol, 60.6 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062
15 mmol) in DMF (10 mL) was added K₂CO₃ (25.7 mg, 0.186 mmol) and (tetrahydro-2H-pyran-4-yl)methyl methanesulfonate (18.07 mg, 0.093 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl
20 acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.016 mmol, 25.5 % yield) as a yellow oil. LCMS (M + H) = 582.2; Retention time (10 mM NH₄HCO₃) = 2.747.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-
25 5'-yl)acetate (30 mg, 0.052 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.19 mg, 0.155 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-

HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (11.8 mg, 0.022 mmol, 42.4 % yield) as white solid. LCMS (M + H) = 540.2; Retention time (10 mM NH_4HCO_3) = 1.509. ^1H NMR (400 MHz, MeOD) δ 8.38 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.57 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.16- 3.85 (m, 4H), 3.51 (t, J = 10.9 Hz, 2H), 3.30- 2.65 (m, 7H), 2.24- 2.07 (m, 1H), 1.83 (d, J = 12.0 Hz, 2H), 1.57- 1.27 (m, 8H), 1.21 (s, 9H), 0.88- 0.76 (m, 6H).

Example 45



(2S)-2-tert-Butoxy-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydrofuran-3-yl)methoxy)-2,3'-bipyridin-5'-yl)acetic acid

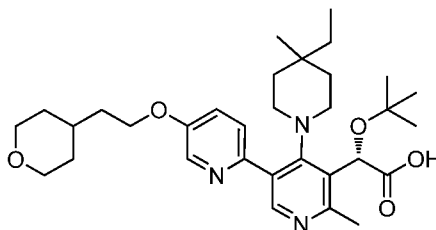
Step 1: To a solution of (tetrahydrofuran-3-yl)methanol (1.9 g, 9.79 mmol) and TEA (1.365 mL, 9.79 mmol) in THF (15 mL) was added dropwise Ms-Cl (0.763 mL, 9.79 mmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred for 20 hours at 25 $^\circ\text{C}$. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 mL), sat NaHCO_3 (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated to give (tetrahydrofuran-3-yl)methyl methanesulfonate (1.2g, 5.92 mmol, 60.5 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added K_2CO_3 (25.7 mg, 0.186 mmol) and (tetrahydrofuran-3-yl)methyl methanesulfonate (22.36 mg, 0.124 mmol). Then, the mixture was stirred for 20 hours at 45 $^\circ\text{C}$ and diluted with water and ethyl acetate (30 mL). Organic layer separated,

washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (35 mg, 0.019 mmol, 31.0 % yield) as a yellow oil. LCMS (M + H) = 568.2; Retention time (10 mM NH₄HCO₃) = 2.451.

Step 3: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (35 mg, 0.062 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (7.40 mg, 0.185 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (15.2 mg, 0.029 mmol, 46.9 % yield) as white solid. LCMS (M + H) = 526.2; Retention time (10 mM NH₄HCO₃) = 1.472. ¹H NMR (400 MHz, MeOD) δ 8.39 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.58 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.19- 4.04 (m, 2H), 3.95 (dt, J = 14.5, 7.4 Hz, 2H), 3.84- 3.69 (m, 2H), 3.23- 2.59 (m, 8H), 2.26- 2.11 (m, 1H), 1.84 (dt, J = 12.9, 7.2 Hz, 1H), 1.65- 1.25 (m, 6H), 1.21 (s, 9H), 0.88- 0.77 (m, 6H).

Example 46



(S)-2-tert-Butoxy-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-2,3'-bipyridin-5'-yl)acetic acid

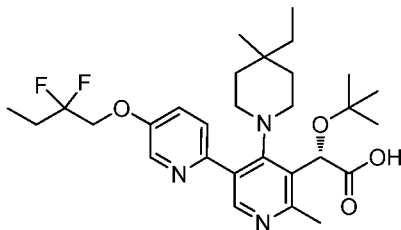
Step 1: To a solution of 2-(tetrahydro-2H-pyran-4-yl)ethan-1-ol (300 mg, 2.304 mmol) and TEA (0.964 mL, 6.91 mmol) in THF (10 mL) was added dropwise Ms-Cl (0.269 mL, 3.46 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃ (10 ml) and brine (10 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated to give 2-(tetrahydro-2H-pyran-4-yl)ethyl methanesulfonate (300 mg, 1.329 mmol, 57.7 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (40 mg, 0.083 mmol) in DMF (10 mL) was added K₂CO₃ (34.3 mg, 0.248 mmol) and 2-(tetrahydro-2H-pyran-4-yl)ethyl methanesulfonate (25.8 mg, 0.124 mmol). The mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.020 mmol, 24.77 % yield) as a yellow oil. LCMS (M + H) = 596.5; Retention time (10 mM NH₄HCO₃) = 2.293.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.086 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.27 mg, 0.257 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (19.0 mg, 0.032 mmol, 37.7 % yield) as white solid. LCMS (M + H) = 554.2; Retention time (10 mM NH₄HCO₃) = 1.545. ¹H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.7 Hz, 1H), 8.17 (s, 1H), 7.57 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.83 (s, 1H), 4.23 (t, J = 6.2 Hz, 2H), 3.97 (dd, J = 11.4, 3.6 Hz, 2H), 3.47 (td, J =

11.8, 2.0 Hz, 2H), 3.30-2.65 (m, 7H), 1.96-1.68 (m, 5H), 1.40-1.39 (m, 8H), 1.21 (s, 9H), 0.90- 0.77 (m, 6H).

Example 47



(S)-2-tert-Butoxy-2-(5-(2,2-difluorobutoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

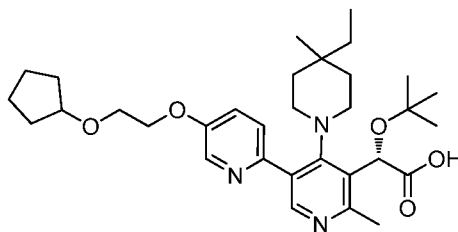
Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added K₂CO₃ (25.7 mg, 0.186 mmol) and 1-bromobutan-2-one (18.73 mg, 0.124 mmol). Then, the mixture was stirred for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product, which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-oxobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (15 mg, 0.027 mmol, 43.7 % yield) as a yellow oil. LCMS (M + H) = 554.4; Retention time (0.01%TFA) = 2.168.

Step 2: The mixture of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-(2-oxobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (15 mg, 0.027 mmol) and DAST (5 mL) was stirred for 20 hours at 20 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄, concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (8 mg, 0.014 mmol, 51.3 % yield) as a yellow oil. LCMS (M + H) = 576.3; Retention time (0.01%TFA) = 2.184.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (8 mg, 0.014 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (1.667 mg,

0.042 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and extracted with ethyl acetate (5 ml). Organic layer concentrated and purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (3.3 mg, 6.18 µmol, 44.5 % yield) as white solid. LCMS (M + H) = 534.2; Retention time (10 mM NH₄HCO₃) = 1.611. ¹H NMR (400 MHz, MeOD) δ 8.45 (d, J = 2.8 Hz, 1H), 8.14 (s, 1H), 7.64 (dd, J = 8.6, 3.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 5.80 (s, 1H), 4.41 (t, J = 12.0 Hz, 2H), 3.31- 2.65 (m, 7H), 2.26- 2.01 (m, 2H), 1.68- 1.25 (m, 6H), 1.20 (s, 9H), 1.12 (t, J = 7.5 Hz, 3H), 0.88-0.75 (m, 6H).

Example 48



(S)-2-tert-Butoxy-2-(5-(2-(cyclopentyloxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-2,3'-bipyridin-5'-yl)acetic acid

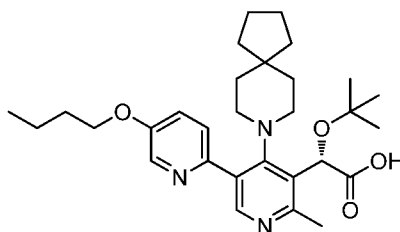
Step 1: To a solution of 2-(cyclopentyloxy)ethan-1-ol (1 g, 7.68 mmol) and TEA (2.141 mL, 15.36 mmol) in THF (15 mL) was added dropwise Ms-Cl (0.898 mL, 11.52 mmol) at 0 °C. The reaction mixture was stirred for 20 hours at 25 °C. The reaction mixture was poured into water (20 mL), extracted by EtOAc (30 mL), washed with 1M HCl (5 ml), sat NaHCO₃, (10 ml) and brine (10 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated to give 2-(cyclopentyloxy)ethyl methanesulfonate (1.07g, 4.62 mmol, 60.2 % yield) as a brown oil which was used in the next step without purification.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added K₂CO₃ (25.7 mg, 0.186 mmol) and 2-(cyclopentyloxy)ethyl methanesulfonate (15.50 mg, 0.074 mmol). The mixture was stirred

for 20 hours at 45 °C and diluted with water and ethyl acetate (30 mL). Organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.046 mmol, 73.8 % yield) as a yellow oil. LCMS (M + H) = 596.4; Retention time (10 mM NH₄HCO₃) = 2.252.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.050 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.04 mg, 0.151 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-[2,3'-bipyridin]-5'-yl)acetic acid (14.4 mg, 0.026 mmol, 51.6 % yield) as white solid. LCMS (M + H) = 554.2; Retention time (10 mM NH₄HCO₃) = 1.654. ¹H NMR (400 MHz, MeOD) δ 8.40 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.60 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.28 (td, J = 3.9, 1.5 Hz, 2H), 4.11- 4.01 (m, 1H), 3.86-3.78 (m, 2H), 3.30- 2.66 (m, 7H), 1.83-1.67 (m, 6H), 1.62-1.44 (m, 4H), 1.41 -1.27 (m, 4H), 1.21 (s, 9H), 0.88- 0.79 (m, 6H).

Example 49

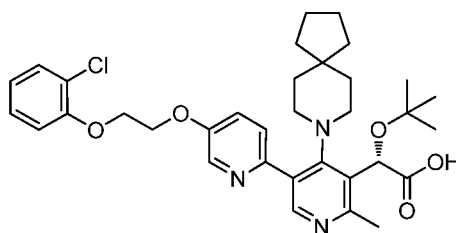


(S)-2-(tert-Butoxy)-2-(5-butoxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (13.94 mg, 0.101 mmol) and 1-bromobutane (13.82 mg, 0.101 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄, concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (44 mg, 0.080 mmol, 79 % yield) as yellow oil. LCMS (M + H) = 552.2; Retention time (10 mM NH₄HCO₃) = 2.905 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (46 mg, 0.083 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.00 mg, 0.250 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (13.1 mg, 0.026 mmol, 30.8 % yield) as white solid. LCMS (M + H) = 510.1; Retention time (10 mM NH₄HCO₃) = 1.736 min. ¹HNMR (400 MHz, MeOD) δ 8.36 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.55 (dd, J = 8.6, 2.9 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 5.84 (s, 1H), 4.16 (t, J = 6.4 Hz, 2H), 3.30- 2.66 (m, 7H), 1.88- 1.83 (m, 2H), 1.64- 1.32 (m, 14H), 1.21 (s, 9H), 1.03- 1.02 (m, 2H).

Example 50

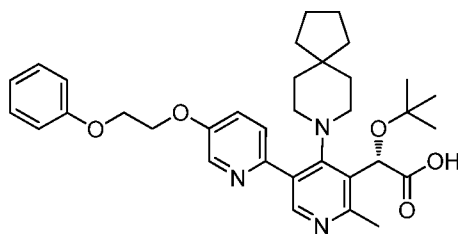


(S)-2-(tert-Butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (69.7 mg, 0.504 mmol) and 2-(2-chlorophenoxy)ethyl methanesulfonate (76 mg, 0.303 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (54 mg, 0.079 mmol, 79 % yield). LCMS (M + H) = 650.0; Retention time (10 mM NH₄HCO₃) = 2.638 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (54 mg, 0.083 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (9.96 mg, 0.249 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (16.7 mg, 0.027 mmol, 33.1 % yield) as white solid. LCMS (M + H) = 608.1; Retention time (10 mM NH₄HCO₃) = 1.619 min. ¹HNMR (400 MHz, MeOD) δ 8.46 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.69 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 7.9, 1.6 Hz, 1H), 7.33- 7.24 (m, 1H), 7.17 (dd, J = 8.3, 1.3 Hz, 1H), 6.97 (td, J = 7.7, 1.4 Hz, 1H), 5.84 (s, 1H), 4.59 (dd, J = 7.0, 3.7 Hz, 2H), 4.51- 4.44 (m, 2H), 3.30- 2.66 (m, 7H), 1.63- 1.47 (m, 8H), 1.47-1.26 (m, 4H), 1.21 (s, 9H).

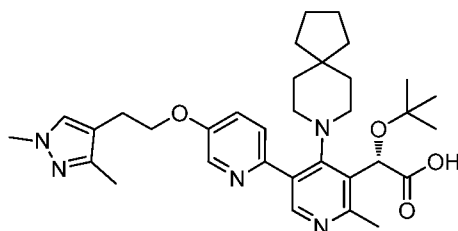
Example 51



(S)-2-(tert-Butoxy)-2-(6'-methyl-5-(2-phenoxyethoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

- 5 Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (69.7 mg, 0.504 mmol) and 2-phenoxyethyl methanesulfonate (65.4 mg, 0.303 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL),
10 dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-5-(2-phenoxyethoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.058 mmol, 57.7 % yield). LCMS (M + H) = 616.2; Retention time (10 mM NH₄HCO₃) = 2.576 min.
- 15 Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-5-(2-phenoxyethoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.084 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.13 mg, 0.253 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer
20 was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(6'-methyl-5-(2-phenoxyethoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-
25 5'-yl)acetic acid (11.9 mg, 0.021 mmol, 24.56 % yield). LCMS (M + H) = 574.2; Retention time (10 mM NH₄HCO₃) = 1.668 min. ¹HNMR (400 MHz, MeOD) δ 8.44 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.64 (dd, J = 8.6, 2.9 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.35- 7.24 (m, 2H), 6.99 (dt, J = 13.5, 4.1 Hz, 3H), 5.84 (s, 1H), 4.53 (dd, J = 6.0, 2.9 Hz, 2H), 4.44- 4.37 (m, 2H), 3.30- 2.66 (m, 7H), 1.68-1.28 (m, 12H), 1.21 (s, 9H).

Example 52



(S)-2-(tert-Butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

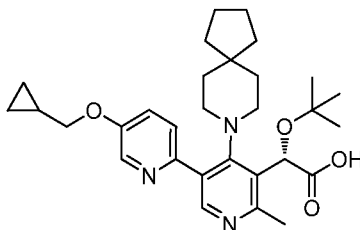
Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 2-(1,3-dimethyl-1H-pyrazol-4-yl)ethyl methanesulfonate (22.02 mg, 0.101 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (42 mg, 0.068 mmol, 67.4 % yield) as yellow oil. LCMS (M + H) = 618.2; Retention time (10 mM NH₄HCO₃) = 2.289 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (42 mg, 0.068 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.16 mg, 0.204 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (17.5 mg, 0.030 mmol, 44.7 % yield) as white solid. LCMS (M + H) = 576.2; Retention time (10 mM NH₄HCO₃) = 1.468

min. ¹HNMR (400 MHz, MeOD) δ 8.37 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.55 (dd, J = 8.6, 2.9 Hz, 1H), 7.45 (d, J = 9.9 Hz, 2H), 5.84 (s, 1H), 4.26 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.22 -2.59 (m, 9H), 2.25 (s, 3H), 1.67-1.27 (m, 12H), 1.21 (s, 9H).

5

Example 53



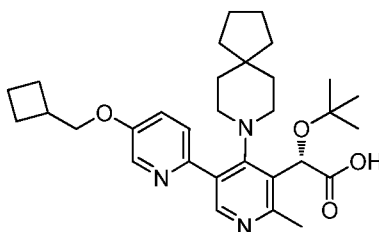
(S)-2-(tert-Butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

10 Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and bromocyclopropane (21.97 mg, 0.182 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over
15 Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.018 mmol, 30.4 % yield) as yellow oil. LCMS (M + H) = 550.3; Retention time (10 mM NH₄HCO₃) = 2.062 min.

20 Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.055 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (2.183 mg, 0.055 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was
25 concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-

bipyridin]-5'-yl)acetic acid (6.2 mg, 0.012 mmol, 22.38 % yield) as white solid. LCMS (M + H) = 508.2; Retention time (10 mM NH₄HCO₃) = 1.596 min. ¹HNMR (400 MHz, MeOD) δ 8.36 (d, J = 2.8 Hz, 1H), 8.16 (s, 1H), 7.54 (dd, J = 8.6, 2.9 Hz, 1H), 7.44 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.01 (d, J = 7.0 Hz, 2H), 3.30- 2.66 (m, 7H), 1.66- 1.27 (m, 13H), 1.21 (s, 9H), 0.72- 0.61 (m, 2H), 0.50- 0.37 (m, 2H).

Example 54



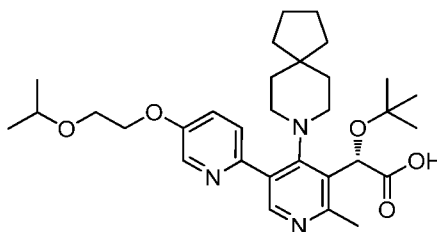
(S)-2-(tert-Butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (32 mg, 0.065 mmol) in DMF (10 mL), K₂CO₃ (8.92 mg, 0.065 mmol) and bromocyclobutane (8.72 mg, 0.065 mmol) was added. The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (32 mg, 0.014 mmol, 22.19 % yield) as yellow oil. LCMS (M + H) = 564.4; Retention time (10 mM NH₄HCO₃) = 2.326 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (32 mg, 0.057 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.81 mg, 0.170 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtime Prep C18 OBD, 21.2 x 250 mm, 10 μm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min;

Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (7.7 mg, 0.015 mmol, 26.0 % yield) as white solid. LCMS (M + H) = 522.2; Retention time (10 mM NH₄HCO₃) = 1.709 min. ¹HNMR (400 MHz, MeOD) δ 8.36 (d, J = 2.8 Hz, 1H), 8.16 (s, 1H), 7.55 (dd, J = 8.6, 2.9 Hz, 1H), 7.44-7.43 (m, 1H), 5.85 (s, 1H), 4.13 (d, J = 6.6 Hz, 2H), 3.30- 2.66 (m, 7H), 2.27- 1.92 (m, 6H), 1.66- 1.28 (m, 13H), 1.21 (s, 9H).

Example 55



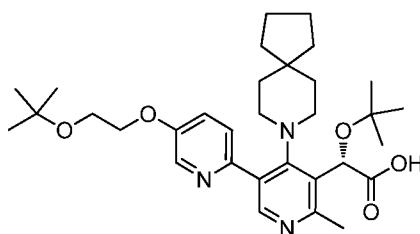
(S)-2-(tert-Butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 2-(2-bromoethoxy)propane (30.3 mg, 0.182 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to isopropyl (S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (27 mg, 0.024 mmol, 39.4 % yield) as yellow oil. LCMS (M + H) = 582.5; Retention time (10 mM NH₄HCO₃) = 2.021 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (27 mg, 0.046 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (5.57 mg, 0.139 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10

µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (16.1 mg, 0.030 mmol, 64.3 % yield) as white solid. LCMS (M + H) = 540.2; Retention time (10 mM NH₄HCO₃) = 1.594 min. ¹HNMR (400 MHz, MeOD) δ 8.40 (d, J = 2.7 Hz, 2H), 8.17 (s, 1H), 7.59 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.32- 4.24 (m, 2H), 3.87 (dd, J = 5.3, 3.8 Hz, 2H), 3.74 (dd, J = 12.2, 6.1 Hz, 1H), 3.30- 2.66 (m, 7H), 1.64- 1.30 (m, 12H), 1.23- 1.21 (m, 15H).

Example 56



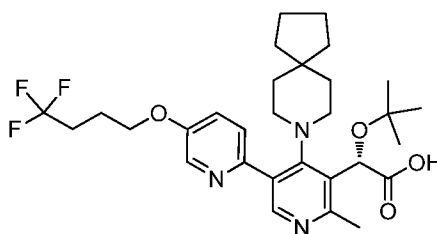
(S)-2-(tert-Butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added 2-(tert-butoxy)ethyl methanesulfonate (23.76 mg, 0.121 mmol) and K₂CO₃ (25.09 mg, 0.182 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (41 mg, 0.023 mmol, 37.2 % yield) as brown oil. LCMS (M + H) = 596.3; Retention time (10 mM NH₄HCO₃) = 2.794 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (41 mg, 0.069 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.26 mg, 0.206 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo,

diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (16 mg, 0.029 mmol, 42.0 % yield) as white solid. LCMS (M + H) = 554.2; Retention time (10 mM NH_4HCO_3) = 1.643 min. ^1H NMR (400 MHz, MeOD) δ 8.40 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.59 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.31- 4.20 (m, 2H), 3.89-3.76 (m, 2H), 3.30- 2.66 (m, 7H), 1.65- 1.49 (m, 8H), 1.47- 1.31 (m, 4H), 1.27 (s, 9H), 1.21 (s, 9H).

Example 57



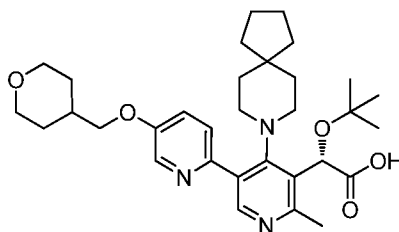
(S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added 4,4,4-trifluorobutyl methanesulfonate (24.96 mg, 0.121 mmol) and K_2CO_3 (25.09 mg, 0.182 mmol). The mixture was stirred for 20 hours at 45 $^\circ\text{C}$, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na_2SO_4 and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (42 mg, 0.026 mmol, 42.4 % yield) as brown oil. LCMS (M + H) = 606.4; Retention time (10 mM NH_4HCO_3) = 2.712 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (42 mg,

0.069 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.32 mg, 0.208 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (17.8 mg, 0.032 mmol, 45.5 % yield) as white solid. LCMS (M + H) = 564.2; Retention time (10 mM NH₄HCO₃) = 1.664 min. ¹HNMR (400 MHz, MeOD) δ 8.40 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.58 (dd, J = 8.6, 2.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.24 (t, J = 6.0 Hz, 2H), 3.30- 2.66 (m, 7H), 2.50- 2.36 (m, 2H), 2.16- 2.09 (m, 2H), 1.66- 1.28 (m, 12H), 1.21 (s, 9H).

Example 58



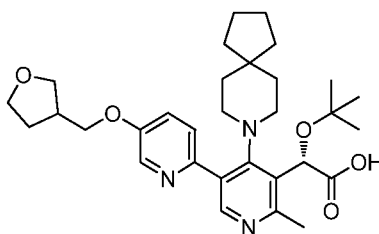
(S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added K₂CO₃ (25.09 mg, 0.182 mmol) and (tetrahydro-2H-pyran-4-yl)methyl methanesulfonate (23.51 mg, 0.121 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-

yl)acetate (32 mg, 0.015 mmol, 24.05 % yield) as yellow oil. LCMS (M + H) = 594.2; Retention time (10 mM NH₄HCO₃) = 2.611 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (32 mg, 0.054 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.47 mg, 0.162 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (6.3 mg, 0.011 mmol, 21.19 % yield) as white solid. LCMS (M + H) = 552.2; Retention time (10 mM NH₄HCO₃) = 1.522 min. ¹HNMR (400 MHz, MeOD) δ 8.37 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.57 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.04- 4.00 (m, 4H), 3.51 (t, J = 11.0 Hz, 2H), 3.30- 2.66 (m, 7H), 2.17-2.16 (m, 1H), 1.83 (d, J = 12.4 Hz, 2H), 1.67- 1.28 (m, 14H), 1.21 (s, 9H).

Example 59



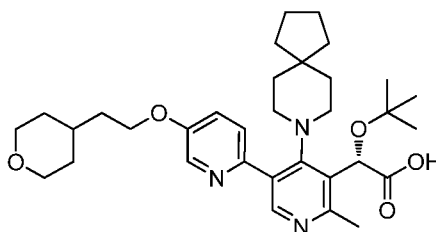
(2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-hydroxy-6'-methyl-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.062 mmol) in DMF (10 mL) was added K₂CO₃ (25.7 mg, 0.186 mmol) and (tetrahydrofuran-3-yl)methyl methanesulfonate (22.36 mg, 0.124 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30

mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-6'-methyl-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (35 mg, 0.019 mmol, 31.0 % yield) as a yellow oil. LCMS (M + H) = 568.2; Retention time (10 mM NH₄HCO₃) = 2.451 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (31 mg, 0.053 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (6.42 mg, 0.160 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (11.8 mg, 0.022 mmol, 41.0 % yield) as white solid. LCMS (M + H) = 538.2; Retention time (10 mM NH₄HCO₃) = 1.487 min. ¹HNMR (400 MHz, MeOD) δ 8.38 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.58 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.85 (s, 2H), 4.23- 4.05 (m, 2H), 3.95 (dt, J = 14.5, 7.4 Hz, 2H), 3.84- 3.71 (m, 2H), 3.30- 2.66 (m, 7H), 2.26 -2.13 (m, 1H), 1.88- 1.80 (m, 1H), 1.68 -1.28 (m, 13H), 1.21 (s, 9H).

Example 60

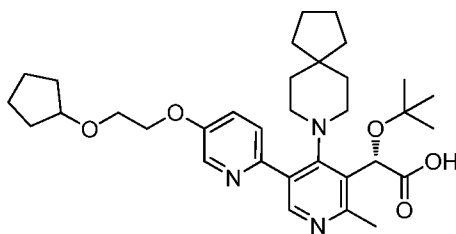


(S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (45 mg, 0.091 mmol) in DMF (10 mL) was added K₂CO₃ (37.6 mg, 0.272 mmol) and 2-(tetrahydro-2H-pyran-4-yl)ethyl methanesulfonate (28.4 mg, 0.136 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.018 mmol, 20.09 % yield) as yellow oil. LCMS (M + H) = 608.5; Retention time (10 mM NH₄HCO₃) = 2.338 min.

Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.086 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.27 mg, 0.257 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (17.0 mg, 0.028 mmol, 32.5 % yield) as white solid. LCMS (M + H) = 566.1; Retention time (10 mM NH₄HCO₃) = 1.562 min. ¹H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.86 (s, 1H), 4.23 (t, J = 6.2 Hz, 2H), 3.97 (dd, J = 11.0, 3.4 Hz, 2H), 3.47 (td, J = 11.9, 2.1 Hz, 2H), 3.30 – 2.66 (m, 7H), 1.93 – 1.29 (m, 19H), 1.21 (s, 9H).

Example 61



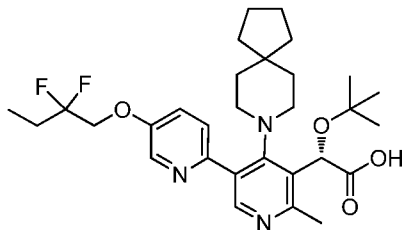
(S)-2-(tert-Butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

- 5 Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added K₂CO₃ (16.73 mg, 0.121 mmol) and 2-(cyclopentyloxy)ethyl methanesulfonate (18.91 mg, 0.091 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL),
 10 washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (28 mg, 0.042 mmol, 69.8 % yield) as yellow oil. LCMS (M + H) = 608.4;
 15 Retention time (10 mM NH₄HCO₃) = 2.400 min.

- Step 2: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (28 mg, 0.046 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (5.53 mg, 0.138 mmol) and stirred for 20 hours at 100 °C. The mixture was
 20 concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the
 25 desired product (S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (8.4 mg, 0.015 mmol, 32.2 % yield) as white solid. LCMS (M + H) = 566.1; Retention time (10 mM NH₄HCO₃) = 1.676 min. ¹HNMR (400 MHz, MeOD) δ 8.40 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.59 (dd, J = 8.6,

2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.85 (s, 1H), 4.32- 4.24 (m, 2H), 4.10- 4.01 (m, 1H), 3.87- 3.80 (m, 2H), 3.30- 2.66 (m, 7H), 1.85-1.28 (m, 20H), 1.21 (s, 9H).

Example 62



(S)-2-(tert-Butoxy)-2-(5-(2,2-difluorobutoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

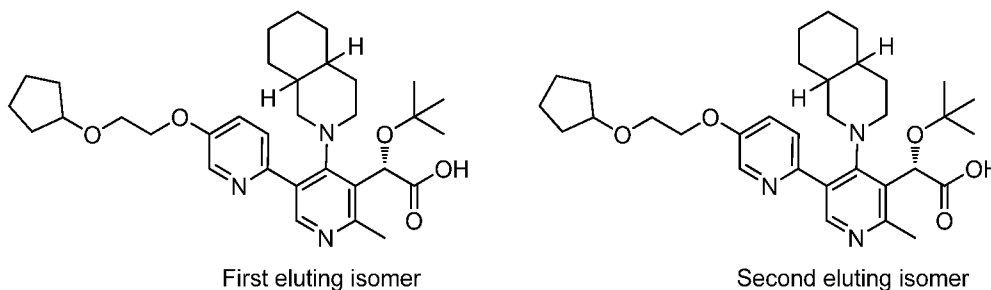
Step 1: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (30 mg, 0.061 mmol) in DMF (10 mL) was added K₂CO₃ (25.09 mg, 0.182 mmol) and 1-bromobutan-2-one (18.28 mg, 0.121 mmol). The mixture was stirred for 20 hours at 45 °C, cooled and diluted with water. The mixture was extracted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-5-(2-oxobutoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (16 mg, 0.028 mmol, 46.7 % yield) as yellow oil. LCMS (M + H) = 566.5; Retention time (0.01%TFA) = 2.202 min.

Step 2: A mixture of isopropyl (S)-2-(tert-butoxy)-2-(6'-methyl-5-(2-oxobutoxy)-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (16 mg, 0.028 mmol) and DAST (5 mL) was stirred for 20 hours at 20 °C. The mixture was diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ethyl acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (9 mg, 0.015 mmol, 54.1 % yield) as yellow oil. LCMS (M + H) = 587.3; Retention time (0.01%TFA) = 2.218 min.

Step 3: To a solution of isopropyl (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy))-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetate (40mg, 0.068 mmol) in

methanol (10 mL) and water (2 mL) was added sodium hydroxide (8.17 mg, 0.204 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml), extracted with ethyl acetate (5 ml) and organic layer was concentrated to give crude product. The crude product was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give the desired product (S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-6'-methyl-4'-(8-azaspiro[4.5]decan-8-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (16.7 mg, 0.030 mmol, 43.9 % yield) as white solid. LCMS (M + H) = 546.2; Retention time (10 mM NH₄HCO₃) = 1.662 min. ¹HNMR (400 MHz, MeOD) δ 8.45 (d, J = 2.8 Hz, 1H), 8.17 (s, 1H), 7.65 (dd, J = 8.6, 3.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 5.86 (s, 1H), 4.42 (t, J = 12.0 Hz, 2H), 3.30- 2.66 (m, 7H), 2.14-2.13 (m, 2H), 1.70- 1.29 (m, 12H), 1.21 (s, 9H), 1.12-1.11 (m, 3H).

Example 63 and 64



(2S)-2-(tert-Butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 2-(cyclopentyloxy)ethyl methanesulfonate (42.0 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.067 mmol, 66.0 %

yield) as yellow oil. LCMS (M + H) = 608.3; Retention time (10 mM NH₄HCO₃) = 2.902 min.

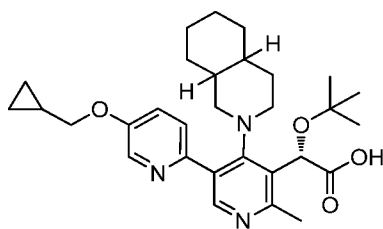
Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.086 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.27 mg, 0.257 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (34.6 mg, 0.061 mmol, 71.5 % yield) as white solid. LCMS (M + H) = 566.2; Retention time (10 mM NH₄HCO₃) = 1.661 min.

Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(2-(cyclopentyloxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (34.6 mg, 0.061 mmol) were separated by SFC [Column AD-H 4.6 x 100 mm 5 µm; Co-Solvent EtOH(1% ammonia/methanol)] to obtain

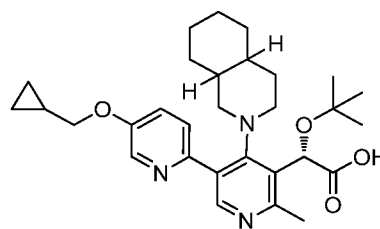
First eluting diastereomer **63**: (8.6 mg, 0.015 mmol, 24.56 % yield). LCMS (M + H) = 566.2; Retention time (10 mM NH₄HCO₃) = 1.673 min. ¹HNMR (400 MHz, MeOD) δ 8.28 (d, J = 2.8 Hz, 1H), 8.01 (s, 1H), 7.48 (dd, J = 8.6, 2.9 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 5.70 (s, 1H), 4.16 (dd, J = 5.3, 3.7 Hz, 2H), 3.94 (ddd, J = 10.0, 6.4, 3.4 Hz, 1H), 3.71 (dd, J = 5.3, 3.7 Hz, 2H), 3.08-1.98 (m, 7H), 1.72- 1.13 (m, 20H), 1.08 (s, 9H) and

Second eluting diastereomer **64**: (7.2 mg, 0.012 mmol, 20.01 % yield). LCMS (M + H) = 566.2; Retention time (10 mM NH₄HCO₃) = 1.661 min. ¹HNMR (400 MHz, MeOD) δ 8.28 (t, J = 4.6 Hz, 1H), 8.03 (s, 1H), 7.48 (dd, J = 8.6, 2.9 Hz, 1H), 7.34 (dd, J = 14.3, 7.6 Hz, 1H), 5.86 (s, 1H), 4.16 (dd, J = 5.3, 3.7 Hz, 2H), 3.93 (ddd, J = 9.8, 6.4, 3.4 Hz, 1H), 3.74- 3.67 (m, 2H), 3.04- 2.42 (m, 5H), 1.95- 1.13 (m, 22H), 1.09 (s, 9H).

Example **65** and **66**



First eluting isomer



Second eluting isomer

2S)-2-(tert-Butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

5 Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and (bromomethyl)cyclopropane (27.2 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.084 mmol, 84 % yield) as yellow oil. LCMS (M + H) = 550.2; Retention time (10 mM NH₄HCO₃) = 2.705 min.

15 Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.095 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (7.57 mg, 0.189 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (34.9 mg, 0.069 mmol, 72.7 % yield) as white solid. LCMS (M + H) = 508.2; Retention time (10 mM NH₄HCO₃) = 1.592 min.

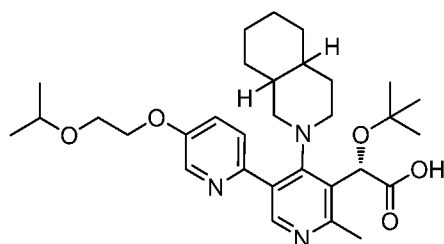
25 Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(cyclopropylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (32.1 mg,

0.063 mmol) were separated by SFC [Column AD-H 4.6 x 100 mm; 5 μ m; Co-Solvent EtOH (1% ammonia/methanol)] to obtain

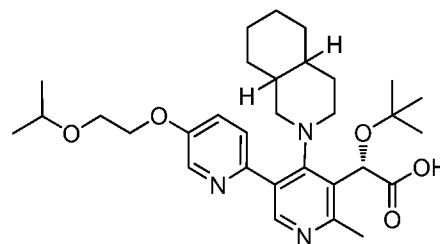
First eluting diastereomer **65**: (9.6 mg, 0.019 mmol, 29.9 % yield). LCMS (M + H) = 508.2; Retention time (10 mM NH₄HCO₃) = 1.605 min. ¹HNMR (400 MHz, MeOD) δ 8.35 (d, J = 2.8 Hz, 1H), 8.11 (s, 1H), 7.54 (dd, J = 8.6, 2.9 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 5.80 (s, 1H), 4.00 (d, J = 7.0 Hz, 2H), 2.66 (s, 3H), 2.31- 1.25 (m, 17H), 1.18 (s, 9H), 0.74- 0.65 (m, 2H), 0.50- 0.34 (m, 2H) and

Second eluting diastereomer **66**: (6.3 mg, 0.012 mmol, 19.63 % yield) . LCMS (M + H) = 508.0; Retention time (10 mM NH₄HCO₃) = 1.595 min. ¹H NMR (400 MHz, MeOD) δ 8.23 (d, J = 2.7 Hz, 1H), 7.98 (s, 1H), 7.42 (dd, J = 8.6, 2.8 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 5.78 (s, 1H), 3.94 – 3.84 (m, 2H), 2.52 (s, 3H), 2.18 -1.12 (m, 17H), 1.07 (s, 9H), 0.62- 0.52 (m, 2H), 0.31 (q, J = 4.6 Hz, 2H).

Example 67 and 68



First eluting isomer



Second eluting isomer

(S)-2-(tert-Butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-(2-(2S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 2-(2-bromoethoxy)propane (33.7 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.091 mmol, 90 %

yield) as yellow oil. LCMS (M + H) = 582.2; Retention time (10 mM NH₄HCO₃) = 2.662 min.

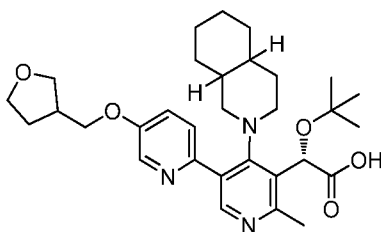
Step 2

- 5 To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.091 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.93 mg, 0.273 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give
- 10 crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (S)-2-(tert-butoxy)-2-(4'-(4-ethyl-4-methylpiperidin-1-yl)-5-(2-(2S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-
- 15 yl)-[2,3'-bipyridin]-5'-yl)acetic acid (32.7 mg, 0.061 mmol, 66.5 % yield) as white solid. LCMS (M + H) = 540.2; Retention time (10 mM NH₄HCO₃) = 1.568 min.

Step 3

- The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(2-isopropoxyethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (32.7 mg, 0.061 mmol)
- 20 were separated by SFC [Column AD-H 4.6 x 100 mmmm 5 µm; Co-Solvent EtOH (1% ammonia/methanol Ammonia)] to obtain.
- First eluting diastereomer **67**: (9.2 mg, 0.017 mmol, 28.1 % yield). LCMS (M + H) = 540.2; Retention time (10 mM NH₄HCO₃) = 1.568 min. ¹HNMR (400 MHz, MeOD) δ
- 25 8.40 (d, J = 2.8 Hz, 1H), 8.14 (s, 1H), 7.60 (dd, J = 8.6, 2.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.28 (dd, J = 5.3, 3.8 Hz, 2H), 3.87 (dd, J = 5.4, 3.7 Hz, 2H), 3.74 (dq, J = 12.2, 6.1 Hz, 1H), 3.17- 2.40 (m, 5H), 1.90 -1.27 (m, 14H), 1.26- 1.16 (m, 15H) and
- Second eluting diastereomer **68**: (8.9 mg, 0.016 mmol, 26.2 % yield) . LCMS (M + H) = 540.2; Retention time (10 mM NH₄HCO₃) = 1.580 min. ¹HNMR (400 MHz, MeOD) δ
- 30 8.29 (d, J = 2.8 Hz, 1H), 8.03 (s, 1H), 7.48 (dd, J = 8.6, 2.9 Hz, 1H), 7.40- 7.30 (m, 1H), 5.74-5.73(m, 2H), 4.19- 4.12 (m, 2H), 3.75 (dd, J = 5.3, 3.8 Hz, 2H), 3.63 (dp, J = 12.3, 6.1 Hz, 1H), 3.07- 2.39 (m, 6H), 1.97-1.15 (m, 13H), 1.13- 1.09 (m, 15H).

Example 69



(2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

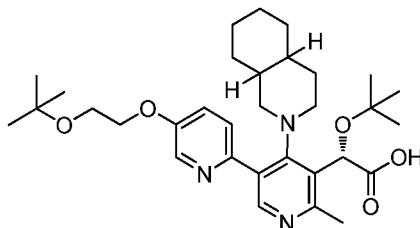
5

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and (tetrahydrofuran-3-yl)methyl methanesulfonate (36.4 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.086 mmol, 86 % yield) as yellow oil. LCMS (M + H) = 580.2; Retention time (10 mM NH₄HCO₃) = 2.474 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.091 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.97 mg, 0.274 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydrofuran-3-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (27.3 mg, 0.050 mmol, 54.2 % yield) as white solid. LCMS (M + H) = 538.2; Retention time (10 mM NH₄HCO₃) = 1.500 min. ¹HNMR (400 MHz, MeOD) δ 8.43- 8.35 (m, 1H), 8.15 (d, J = 10.1 Hz, 1H), 7.59 (dt, J = 8.6, 2.8 Hz, 1H),

7.52- 7.41 (m, 1H), 5.82 (s, 1H), 4.12 (ddd, J = 19.9, 13.1, 7.8 Hz, 2H), 3.94 (qd, J = 7.4, 2.2 Hz, 2H), 3.86 -3.71 (m, 2H), 3.28- 2.57 (m, 8H), 2.26- 1.26 (m, 14H), 1.20 (s, 9H).

Example 70



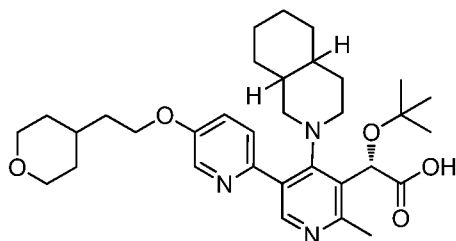
(2S)-2-(tert-Butoxy)-2-(5-(2-(tert-butoxy)ethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL), was added 2-(tert-butoxy)ethyl methanesulfonate (39.6 mg, 0.202 mmol) and K₂CO₃ (41.8 mg, 0.303 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.081 mmol, 80 % yield) as brown oil. LCMS (M + H) = 596.3; Retention time (10 mM NH₄HCO₃) = 2.786 min.

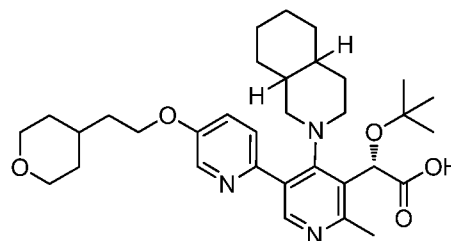
Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.086 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.27 mg, 0.257 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(2-(tert-butoxy)ethoxy))-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-

yl)acetic acid (29 mg, 0.051 mmol, 59.8 % yield) as white solid. LCMS (M + H) = 554.2; Retention time (10 mM NH₄HCO₃) = 1.631 min. ¹HNMR (400 MHz, MeOD) δ 8.40 (t, J = 3.3 Hz, 1H), 8.14 (d, J = 5.0 Hz, 1H), 7.60 (dd, J = 8.6, 2.8 Hz, 1H), 7.47 (dd, J = 8.6, 5.6 Hz, 1H), 5.81 (s, 1H), 4.31- 4.21 (m, 2H), 3.87 -3.75 (m, 2H), 3.18- 2.58 (m, 5H), 2.14- 1.10 (m, 32H).

Example 71 and 72



First eluting isomer



Second eluting isomer

(2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 2-(tetrahydro-2H-pyran-4-yl)ethyl methanesulfonate (31.5 mg, 0.151 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.082 mmol, 81 % yield) as yellow oil. LCMS (M + H) = 608.2; Retention time (10 mM NH₄HCO₃) = 2.649 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.086 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.27 mg, 0.257 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give crude product which was purified by

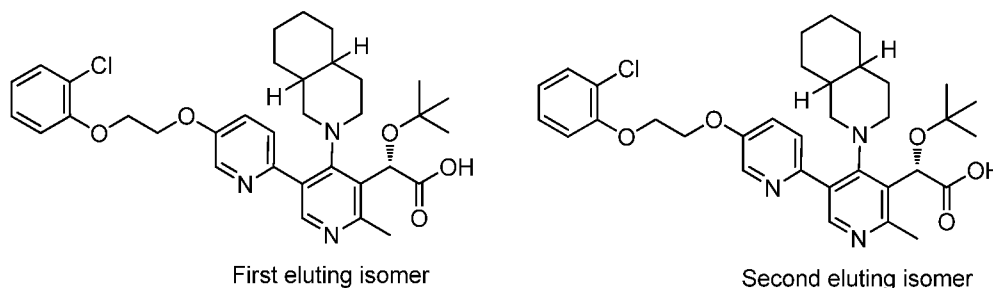
Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (21.5 mg, 0.038 mmol, 44.4 % yield) as white solid. LCMS (M + H) = 566.2; Retention time (10 mM NH_4HCO_3) = 1.560 min.

Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-(tetrahydro-2H-pyran-4-yl)ethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (21.5 mg, 0.038 mmol) were separated by SFC [Column IC (4.6 x 100 mm; 5 μ m); Co-Solvent MeOH (0.2% ammonia/methano)] to obtain

First eluting diastereomer **71**: (4.5 mg, 7.70 μ mol, 20.27 % yield). LCMS (M + H) = 566.1; Retention time (10 mM NH_4HCO_3) = 1.558 min. ^1H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.8 Hz, 1H), 8.13 (s, 1H), 7.57 (dd, J = 8.6, 2.9 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H), 5.82 (s, 1H), 4.23 (t, J = 6.2 Hz, 2H), 3.97 (dd, J = 11.1, 3.4 Hz, 2H), 3.47 (td, J = 11.9, 1.9 Hz, 2H), 2.66 (s, 3H), 1.93- 1.29 (m, 23H), 1.20 (s, 9H) and

Second eluting diastereomer **72**: (3.7 mg, 6.54 μ mol, 17.21 % yield). LCMS (M + H) = 566.2 ; Retention time (10 mM NH_4HCO_3) = 1.545 min. ^1H NMR (400 MHz, MeOD) δ 8.26 (d, J = 2.7 Hz, 1H), 8.03 (s, 1H), 7.45 (dd, J = 8.6, 2.9 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 5.83 (s, 1H), 4.11 (t, J = 6.1 Hz, 2H), 3.85 (dd, J = 10.9, 3.7 Hz, 2H), 3.34 (td, J = 11.9, 2.0 Hz, 2H), 2.52 (s, 3H), 2.13- 2.07 (m, 1H), 1.98- 1.16 (m, 23H), 1.08 (s, 9H).

Example 73 and 74



(2S)-2-(tert-Butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10

mL) was added K_2CO_3 (69.7 mg, 0.504 mmol) and 2-(2-chlorophenoxy)ethyl methanesulfonate (76 mg, 0.303 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na_2SO_4 and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.065 mmol, 64.7 % yield) as yellow oil. LCMS (M + H) = 650.1; Retention time (10 mM NH_4HCO_3) = 2.742 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.077 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (9.23 mg, 0.231 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (36.5 mg, 0.060 mmol, 78 % yield) as white solid. LCMS (M + H) = 608.1; Retention time (10 mM NH_4HCO_3) = 1.687 min.

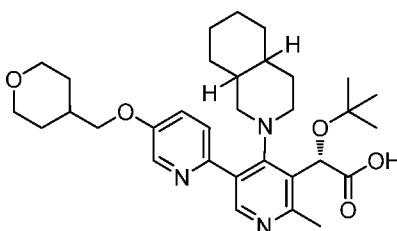
Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(2-(2-chlorophenoxy)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (36.5 mg, 0.060 mmol) were separated by SFC [Column IC (4.6 x 100 mm; 5 μ m); Co-Solvent MeOH (0.2% ammonia/methanol)].

First eluting diastereomer **73**: (3.9 mg, 6.41 μ mol, 10.68 % yield). LCMS (M + H) = 608.1; Retention time (10 mM NH_4HCO_3) = 1.662 min. 1H NMR (400 MHz, MeOD) δ 8.47 (d, J = 2.8 Hz, 1H), 8.16 (d, J = 9.3 Hz, 1H), 7.70 (dd, J = 8.6, 2.9 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 7.9, 1.6 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.17 (dd, J = 8.3, 1.3 Hz, 1H), 6.97 (td, J = 7.7, 1.4 Hz, 1H), 5.96 (s, 1H), 4.62– 4.55 (m, 2H), 4.50– 4.44 (m, 2H), 2.66 (s, 3H), 2.24–2.17 (m, 1H), 2.10– 1.99 (m, 1H), 1.91–1.29 (m, 14H), 1.21 (s, 9H) and Second eluting diastereomer **74**: (4.1 mg, 6.74 μ mol, 11.23 % yield). LCMS (M + H) = 608.1; Retention time (10 mM NH_4HCO_3) = 1.669 min. 1H NMR (400 MHz, MeOD) δ 8.33 (d, J

= 2.8 Hz, 1H), 8.01 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.26 (dd, J = 7.9, 1.6 Hz, 1H), 7.20- 7.14 (m, 1H), 7.05 (dd, J = 8.3, 1.3 Hz, 1H), 6.85 (td, J = 7.7, 1.4 Hz, 1H), 5.67 (s, 1H), 4.46 (dd, J = 5.4, 3.1 Hz, 2H), 4.35 (dd, J = 5.4, 3.1 Hz, 2H), 2.57 (s, 3H), 2.00- 1.87 (m, 1H), 1.72- 1.14 (m, 15H), 1.07 (s, 9H).

5

Example 75



(2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

10

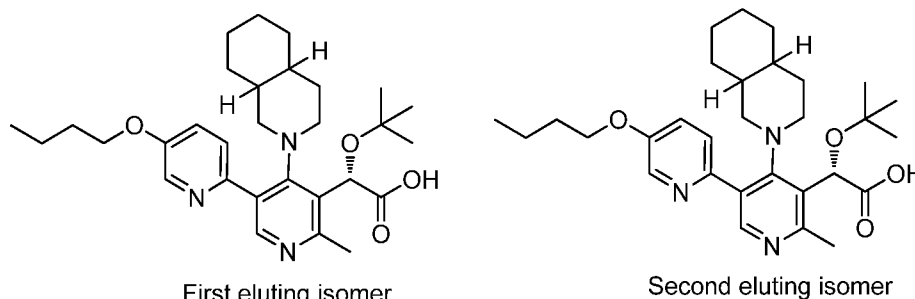
Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and (tetrahydro-2H-pyran-4-yl)methyl methanesulfonate (29.4 mg, 0.151 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.085 mmol, 84 % yield) as yellow oil. LCMS (M + H) = 594.2; Retention time (10 mM NH₄HCO₃) = 2.565 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetate (53 mg, 0.089 mmol) in methanol (10 mL) and water (2 mL) was added NaOH (10.71 mg, 0.268 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0

min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-((tetrahydro-2H-pyran-4-yl)methoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (3.9 mg, 6.84 μ mol, 7.66 % yield) as white solid. LCMS (M + H) = 552.2 ; Retention time (10 mM NH₄HCO₃) = 1.522 min. ¹HNMR (400 MHz, MeOD)

5 δ 8.40 – 8.34 (m, 1H), 8.13 (d, J = 9.5 Hz, 1H), 7.62 – 7.53 (m, 1H), 7.50 – 7.42 (m, 1H), 5.96 (s, 1H), 4.09- 3.97 (m, 4H), 3.51 (t, J = 11.7 Hz, 2H), 3.18- 2.58 (m, 5H), 2.23-1.26 (m, 19H), 1.20 (s, 9H).

Example 76 and 77



(2S)-2-(tert-Butoxy)-2-(5-butoxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and 1-bromobutane (27.6 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.026 mmol, 25.6 % yield) as yellow oil. LCMS (M + H) = 552.4; Retention time (10 mM NH₄HCO₃) = 1.787 min.

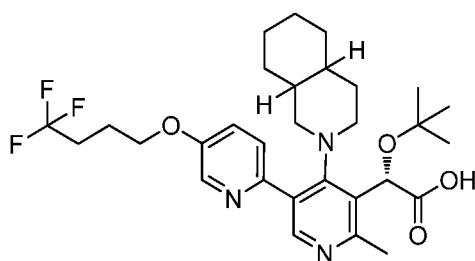
Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (52 mg, 0.094 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (3.77 mg, 0.094 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give

crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 μ m; Mobile Phase A: Water (10 mM NH_4HCO_3); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-

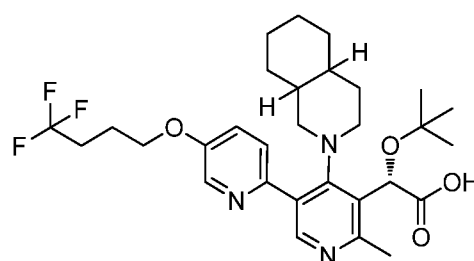
- 5 (octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (28.8 mg, 0.057 mmol, 60.0 % yield) as white solid. LCMS (M + H) = 510.1; Retention time (10 mM NH_4HCO_3) = 1.687 min.

- Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-butoxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (28.8 mg, 0.057 mmol) were separated by SFC [Column AD-H (4.6 x 100 mm; 5 μ m); Co-Solvent EtOH(1.0% ammonia/methanol)] to obtain
- 10 First eluting diastereomer **76**: (4.3 mg, 8.05 μ mol, 14.24 % yield). LCMS (M + H) = 510.1; Retention time (10 mM NH_4HCO_3) = 1.663 min. ^1H NMR (400 MHz, MeOD) δ 8.23 (d, J = 2.8 Hz, 1H), 8.02 (d, J = 9.4 Hz, 1H), 7.43 (dd, J = 8.6, 2.9 Hz, 1H), 7.34 (d, J = 8.6 Hz, 1H), 5.69 (s, 1H), 4.04 (t, J = 6.4 Hz, 2H), 2.53 (d, J = 9.1 Hz, 3H), 1.78- 1.15 (m, 20H), 1.08 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H) and
- 15 Second eluting diastereomer **77**: (2.7 mg, 4.87 μ mol, 8.62 % yield). LCMS (M + H) = 510.1; Retention time (10 mM NH_4HCO_3) = 1.657 min. ^1H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.56 (dd, J = 8.6, 2.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.97 (s, 1H), 4.17 (t, J = 6.4 Hz, 2H), 2.64 (s, 3H), 2.42 – 1.23 (m, 20H), 1.21 (s, 9H), 1.03 (t, J = 7.4 Hz, 3H).
- 20

Example 78 and 79



First eluting isomer



Second eluting isomer

- 25 (2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL), was added K₂CO₃ (41.8 mg, 0.303 mmol) and 4,4,4-trifluorobutyl methanesulfonate (41.6 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.080 mmol, 80 % yield) as brown oil. LCMS (M + H) = 606.2; Retention time (10 mM NH₄HCO₃) = 2.688 min.

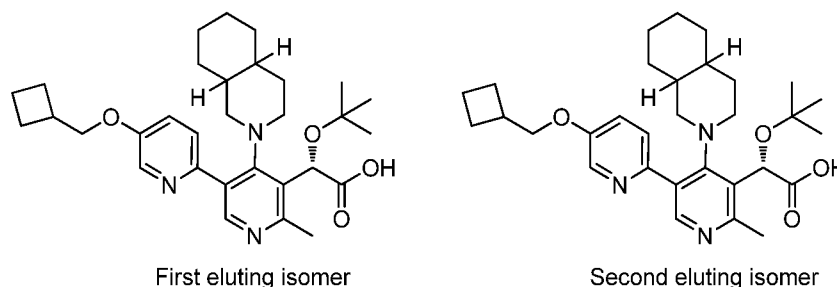
Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetate (51 mg, 0.084 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.10 mg, 0.253 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (32.5 mg, 0.058 mmol, 68.5 % yield) as white solid. LCMS (M + H) = 564.1; Retention time (10 mM NH₄HCO₃) = 1.651 min.

Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(4,4,4-trifluorobutoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (32.5 mg, 0.058 mmol) were separated by SFC (Column IC (4.6 x 100 mm; 5 µm); Co-Solvent MeOH (0.2% ammonia/methanol)] to obtain First eluting diastereomer **78**: (4.8 mg, 8.38 µmol, 14.53 % yield). LCMS (M + H) = 564.2; Retention time (10 mM NH₄HCO₃) = 1.629 min. ¹HNMR (400 MHz, MeOD) δ 8.38 (d, J = 2.8 Hz, 1H), 8.07 (s, 1H), 7.57 (dd, J = 8.6, 2.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.87 (s, 1H), 4.23 (t, J = 6.0 Hz, 2H), 3.28- 2.88 (m, 2H), 2.64 (s, 3H), 2.50- 2.36 (m, 2H), 2.15- 2.04 (m, 2H), 1.89- 1.24 (m, 14H), 1.18 (s, 9H) and Second eluting diastereomer **79**: (4.4 mg, 7.70 µmol, 13.35 % yield). LCMS (M + H) = 564.2; Retention time (10 mM NH₄HCO₃) = 1.640 min. ¹HNMR (400 MHz, MeOD) δ 8.36

(d, J = 2.8 Hz, 1H), 8.06 (s, 1H), 7.57 (dd, J = 8.6, 2.9 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 5.75 (s, 1H), 4.23 (t, J = 6.1 Hz, 2H), 3.29 – 3.00 (m, 2H), 2.65 (s, 3H), 2.53- 2.35 (m, 2H), 2.15- 2.04 (m, 2H), 1.82 -1.23 (m, 14H), 1.17 (s, 9H).

5

Example 80 and 81



(2S)-2-(tert-Butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

10 Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (41.8 mg, 0.303 mmol) and (bromomethyl)cyclobutane (30.1 mg, 0.202 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄

15 and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.079 mmol, 79 % yield) as yellow oil. LCMS (M + H) = 564.4; Retention time (0.01% TFA) = 1.800 min.

20 Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.089 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (10.64 mg, 0.266 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and

25 concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-

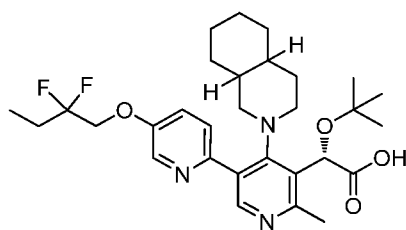
methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (29.5 mg, 0.057 mmol, 63.8 % yield) as white solid. LCMS (M + H) = 522.2; Retention time (10 mM NH₄HCO₃) = 1.705 min.

Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(cyclobutylmethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (29.5 mg, 0.057 mmol) were separated by SFC [Column AD-H (4.6 x 100 mm; 5 μm); Co-Solvent EtOH (1.0% ammonia/methanol)] to obtain

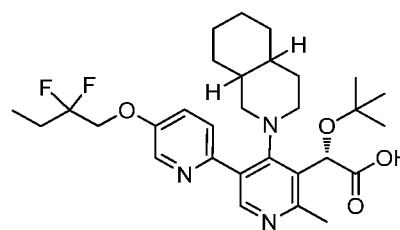
First eluting diastereomer **80**: (4.3 mg, 8.13 μmol, 14.37 % yield). LCMS (M + H) = 522.2; Retention time (10 mM NH₄HCO₃) = 1.685 min. ¹H NMR (400 MHz, MeOD) δ 8.24 (d, J = 2.8 Hz, 1H), 8.01 (s, 1H), 7.44 (dd, J = 8.6, 2.9 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 5.69 (s, 1H), 4.00 (d, J = 6.5 Hz, 2H), 3.11- 2.46 (m, 5H), 2.22- 1.12 (m, 21H), 1.08 (s, 9H) and

Second eluting diastereomer **81**: (4.4 mg, 8.43 μmol, 14.92 % yield). LCMS (M + H) = 522.2; Retention time (10 mM NH₄HCO₃) = 1.686 min. ¹H NMR (400 MHz, MeOD) δ 8.37 (d, J = 2.8 Hz, 1H), 8.16 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.97 (s, 1H), 4.13 (d, J = 6.6 Hz, 2H), 3.24- 2.60 (m, 5H), 2.26- 1.25 (m, 21H), 1.21 (s, 9H).

Example **82** and **83**



First eluting isomer



Second eluting isomer

(2S)-2-(tert-Butoxy)-2-(5-(2,2-difluorobutoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (80 mg, 0.161 mmol) in DMF (10 mL) was added K₂CO₃ (66.9 mg, 0.484 mmol) and 1-bromobutan-2-one (48.7 mg, 0.323 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford 5'-

((S)-1-(tert-butoxy)-2-isopropoxy-2-oxoethyl)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5-yl butyrate (72 mg, 0.050 mmol, 31.0 % yield) as yellow oil. LCMS (M + H) = 566.3; Retention time (0.01%TFA) = 2.028 min.

Step 2: A solution of 5'-((S)-1-(tert-butoxy)-2-isopropoxy-2-oxoethyl)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5-yl butyrate (72 mg, 0.127 mmol) in DAST (5 mL) was stirred for 20 hours at 20 °C. The mixture was diluted with ethyl acetate (30 mL), washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(1,1-difluorobutoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (60 mg, 0.096 mmol, 76 % yield). LCMS (M + H) = 588.3; Retention time (0.01%TFA) = 2.178 min.

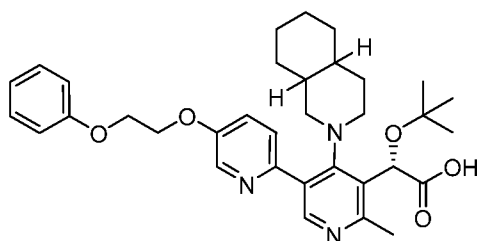
Step 3: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (60mg, 0.102 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (12.25 mg, 0.306 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (47.8 mg, 0.088 mmol, 86 % yield) as white solid. LCMS (M + H) = 546.2 ; Retention time (10 mM NH₄HCO₃) = 1.621 min.

Step 4: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(2,2-difluorobutoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (47.8 mg, 0.088 mmol) were separated by SFC [Column IC (4.6 x 100 mm; 5 µm); Co-Solvent MeOH (0.2% ammonia/methanol)] to obtain

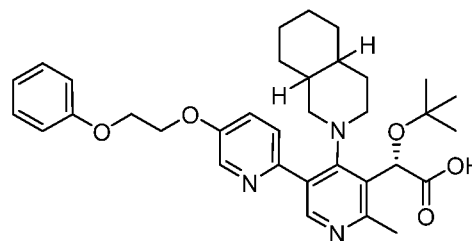
First eluting diastereomer **82**: (4.8 mg, 8.05 µmol, 9.19 % yield). LCMS (M + H) = 546.2 ; Retention time (10 mM NH₄HCO₃) = 1.604 min. ¹HNMR (400 MHz, MeOD) δ 8.46 (d, J = 2.8 Hz, 1H), 8.16 (s, 1H), 7.66 (dd, J = 8.6, 3.0 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 5.98 (s, 1H), 4.42 (t, J = 12.0 Hz, 2H), 3.28 – 2.83 (m, 2H), 2.65 (s, 3H), 2.21- 2.06 (m, 2H), 1.90-1.27 (m, 14H), 1.20 (s, 9H), 1.12 (t, J = 7.5 Hz, 3H) and

Second eluting diastereomer **83**: (4.9 mg, 8.33 μ mol, 9.51 % yield). LCMS (M + H) = 546.2 ; Retention time (10 mM NH₄HCO₃) = 1.614 min. ¹HNMR (400 MHz, MeOD) δ 8.45 (d, J = 2.8 Hz, 1H), 8.14 (s, 1H), 7.65 (dd, J = 8.6, 3.0 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 5.83 (s, 1H), 4.41 (t, J = 12.0 Hz, 2H), 3.20 – 2.81 (m, 2H), 2.65 (s, 3H), 2.24- 2.02 (m, 2H), 1.80- 1.32(m, 14H), 1.20 (s, 9H), 1.12 (t, J = 7.5 Hz, 3H).

Example **84** and **85**



First eluting isomer



Second eluting isomer

(2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in (10 mL) was added K₂CO₃ (69.7 mg, 0.504 mmol) and 2-phenoxyethyl methanesulfonate (65.4 mg, 0.303 mmol) . The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.049 mmol, 49.0 % yield) as yellow oil. LCMS (M + H) = 616.2; Retention time (10 mM NH₄HCO₃) = 2.679 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.081 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (9.74 mg, 0.244 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 ml) and ethyl acetate (5ml). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10

µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (ml/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (28.5 mg, 0.050 mmol, 61.2 % yield) as white solid and mixture of

5 diastereomers. LCMS (M + H) = 574.2; Retention time (10 mM NH₄HCO₃) = 1.634 min.

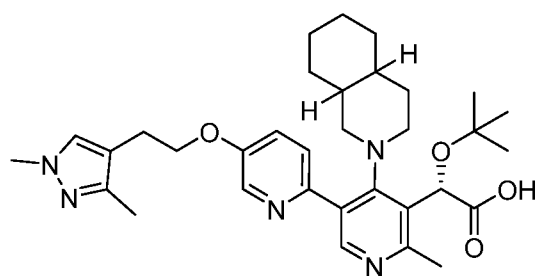
Step 3: The diastereomers of (2S)-2-(tert-Butoxy)-2-(6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-5-(2-phenoxyethoxy)-[2,3'-bipyridin]-5'-yl)acetic acid (28.5 mg, 0.050 mmol) were separated by SFC [Column AD-H 4.6 x 100 mm mm 5 µm; Co-Solvent EtOH (1% ammonia/methanol)].

10 First eluting diastereomer **84**: (4.6 mg, 7.69 µmol, 15.48 % yield). LCMS (M + H) = 574.1; Retention time (10 mM NH₄HCO₃) = 1.638 min. ¹HNMR (400 MHz, MeOD) δ 8.44 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H), 7.65 (dd, J = 8.6, 2.9 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.35-7.26 (m, 2H), 6.98 (dd, J = 14.2, 7.6 Hz, 3H), 5.82 (s, 1H), 4.52 (dd, J = 5.4, 3.3 Hz, 2H), 4.41 (dd, J = 5.4, 3.3 Hz, 2H), 2.67 (s, 3H), 2.29- 1.28 (m, 16H), 1.22 (s, 9H) and

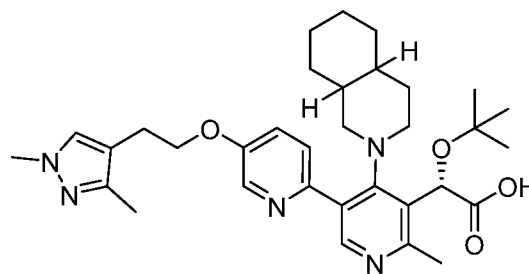
15 Second eluting diastereomer **85**: (4.7 mg, 8.19 µmol, 16.49 % yield). LCMS (M + H) = 574.2; Retention time (10 mM NH₄HCO₃) = 1.630 min. ¹HNMR (400 MHz, MeOD) δ 8.45 (d, J = 2.9 Hz, 1H), 8.17 (s, 1H), 7.65 (dd, J = 8.5, 2.9 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.35- 7.24 (m, 2H), 7.03- 6.91 (m, 3H), 4.53 (dd, J = 5.9, 2.8 Hz, 2H), 4.41 (dd, J = 5.3, 3.4 Hz, 2H), 2.64 (s, 3H), 2.25- 1.27 (m, 16H), 1.21 (s, 9H).

20

Example 86 and 87



First eluting isomer



Second eluting isomer

(2S)-2-(tert-Butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid

25

Step 1: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-hydroxy-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.101 mmol) in DMF (10 mL) was added K₂CO₃ (69.7 mg, 0.504 mmol) and 2-(1,3-dimethyl-1H-pyrazol-

4-yl)ethyl methanesulfonate (66.1 mg, 0.303 mmol). The mixture was stirred for 20 hours at 45 °C, diluted with water and ethyl acetate (30 mL), organic layer separated, washed with brine (20 mL), dried over Na₂SO₄ and concentrated to obtain a crude product which was purified by silica gel chromatography eluting with ether acetate/ petroleum ether (from 10:1 to 1:1) to afford isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.048 mmol, 47.3 % yield) as yellow oil. LCMS (M + H) = 618.2; Retention time (10 mM NH₄HCO₃) = 2.363 min.

Step 2: To a solution of isopropyl (2S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetate (50 mg, 0.081 mmol) in methanol (10 mL) and water (2 mL) was added sodium hydroxide (9.71 mg, 0.243 mmol) and stirred for 20 hours at 100 °C. The mixture was concentrated under vacuo, diluted with HCl (1N, 0.5 mL) and ethyl acetate (5 mL). Organic layer separated and concentrated to give crude product which was purified by Prep-HPLC {Instrument Gilson 281 (PHG-009); Column Xtimate Prep C18 OBD, 21.2 x 250 mm, 10 µm; Mobile Phase A: Water (10 mM NH₄HCO₃); B: MeCN; Gradient 40-68%B in 8.0 min, stop at 13.0 min; Flow Rate (mL/min) 30.00} to give (2S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (29.2 mg, 0.051 mmol, 62.7 % yield) as white solid. LCMS (M + H) = 576.2; Retention time (10 mM NH₄HCO₃) = 1.465 min.

Step 3: The diastereomers of (2S)-2-(tert-butoxy)-2-(5-(2-(1,3-dimethyl-1H-pyrazol-4-yl)ethoxy)-6'-methyl-4'-(octahydroisoquinolin-2(1H)-yl)-[2,3'-bipyridin]-5'-yl)acetic acid (29.2 mg, 0.051 mmol) were separated by SFC [Column AD-H 4.6 x 100 mm; 5 µm; Co-Solvent EtOH (1% ammonia/methanol)] to obtain

First eluting diastereomer **86**: (4.2 mg, 7.08 µmol, 13.97 % yield). LCMS (M + H) = 576.2; Retention time (10 mM NH₄HCO₃) = 1.476 min. ¹H NMR (400 MHz, MeOD) δ 8.36 (d, J = 2.8 Hz, 1H), 8.11 (s, 1H), 7.56 (dd, J = 8.6, 2.9 Hz, 1H), 7.45 (d, J = 9.0 Hz, 2H), 5.81 (s, 1H), 4.25 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 3.28- 2.78 (m, 4H), 2.66 (s, 3H), 2.25 (s, 3H), 1.86-1.30 (m, 14H), 1.19 (s, 9H) and

Second eluting diastereomer **87**: (4.5 mg, 7.47 µmol, 14.73 % yield). LCMS (M + H) = 576.2; Retention time (10 mM NH₄HCO₃) = 1.467 min. ¹H NMR (400 MHz, MeOD) δ 8.26 (d, J = 2.7 Hz, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 8.6, 2.9 Hz, 1H), 7.34 (t, J =

11.4 Hz, 2H), 5.86 (s, 1H), 4.14 (t, J = 6.6 Hz, 2H), 3.68 (s, 3H), 3.15- 2.59 (m, 7H), 2.52 (s, 3H), 2.13 (s, 3H), 1.79-1.16 (m, 14H), 1.09 (s, 9H).

Biological Methods

5

Inhibition of HIV replication: A recombinant NL-RLuc proviral clone was constructed in which a section of the nef gene from NL4-3 was replaced with the *Renilla* Luciferase gene. This virus is fully infectious and can undergo multiple cycles of replication in cell culture. In addition, the luciferous reporter provides a simple and easy method for quantitating the extent of virus growth and consequently, the antiviral activity of test compounds. The plasmid pNLRLuc contains the proviral NL-RLuc DNA cloned into pUC18 at the *PvuII* site. The NL-RLuc virus was prepared by transfection of 293T cells with the plasmid pNLRLuc. Transfections were performed using the LipofectAMINE PLUS kit from Invitrogen (Carlsbad, CA) according to the manufacturer and the virus generated was titrated in MT-2 cells. For susceptibility analyses, the titrated virus was used to infect MT-2 cells in the presence of compound, and after 5 days of incubation, cells were processed and quantitated for virus growth by the amount of expressed luciferase. Assay media was RPMI 1640 supplemented with 10% heat inactivated fetal bovine serum (FBS), 100 units/ml penicillin G/100 units/ml streptomycin, 10 mM HEPES buffer pH 7.55 and 2 mM L-glutamine. The results from at least 2 experiments were used to calculate the EC₅₀ values. Luciferase was quantitated using the Dual Luciferase kit from Promega (Madison, WI). Susceptibility of viruses to compounds was determined by incubation in the presence of serial dilutions of the compound. The 50% effective concentration (EC₅₀) was calculated by using the exponential form of the median effect equation where $(Fa) = 1/[1 + (ED_{50}/\text{drug conc.})^m]$ (Johnson VA, Byington RT. Infectivity Assay. In *Techniques in HIV Research*. ed. Aldovini A, Walker BD. 71-76. New York: Stockton Press.1990).

Results are summarized in Table 1.

Table 1.

Example	EC ₅₀ μ M
1	36.1
2	3
3	134
4	3.1
5	18.3
6	9.4
7	6.7
8	14.8
9	21.3
10	10.7
11	23.4
12	22.3
13	6.5
14	11.9
15	14.4
16	17.6
17	36
18	2.9
19	43.2
20	ND
21	46.3
22	10.6
23	43.1
24	0.8
25	3.7
26	0.6
27	11.7
28	1.7
29	0.7
30	8.7

Example	EC ₅₀ μM
31	3.5
32	3.8
33	1.6
34	123.2
35	7.1
36	1.9
37	2.6
38	4.4
39	4.2
40	4.4
41	2.9
42	2.1
43	2.8
44	2
45	3.9
46	1.3
47	4.6
48	0.9
49	4.5
50	52.5
51	5
52	4.9
53	9.8
54	14.5
55	6.3
56	5
57	7.1
58	8.1
59	7.6
60	1
61	2.3

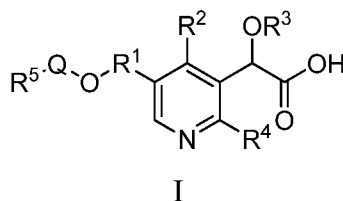
Example	EC ₅₀ μ M
62	9
63	0.7
64	21.2
65	1.9
66	34.2
67	1.8
68	46.9
69	4.9
70	4.9
71	1.3
72	14.8
73	11.6
74	1.6
75	5.6
76	2.6
77	31.8
78	114.8
79	4.4
80	4.7
81	92.1
82	61.1
83	4.8
84	0.9
85	24.6
86	3.5
87	20.9

ND: Not determined

CLAIMS

We claim:

1. A compound of Formula I, or a pharmaceutically acceptable salt thereof,



wherein R³ is C₁₋₈alkyl;

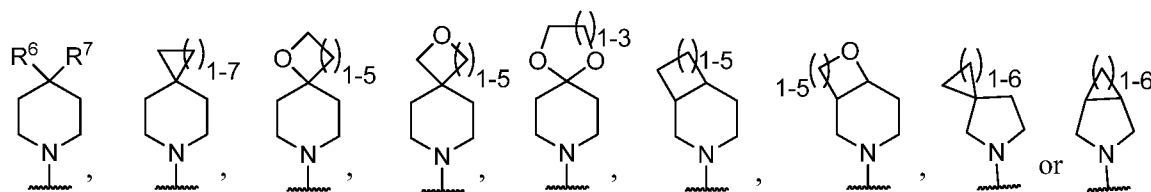
R⁴ is C₁₋₄alkyl;

R¹ is pyridinyl or phenyl and is optionally substituted with 1 or 2 halogens;

Q is C₁₋₆alkyl optionally substituted with 1 to 3 halogens;

R⁵ is H, halo, phenyl, phenyl-O-, C₃₋₆cycloalkyl, C₃₋₆cycloalkyl-O-, C₁₋₆alkyl-O-, pyrazolyl, tetrahydropyranyl, or tetrahydrofuryl, and is optionally substituted with 1-3 substituents independently selected from halogen and C₁₋₆alkyl;

R² is



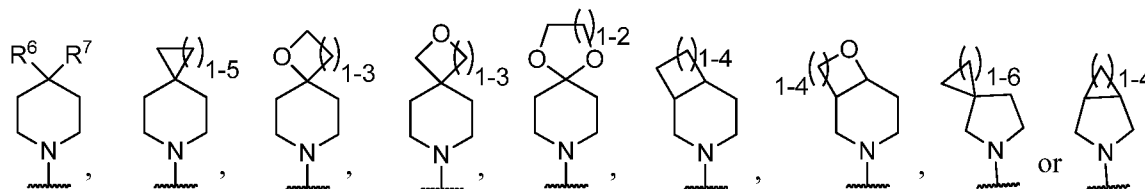
wherein R⁶ is C₁₋₆alkyl; R⁷ is C₂₋₆alkyl, phenyl, -OC₁₋₆alkyl, CN, or halogen; and R² is optionally substituted with 1-3 substituents independently selected from halogen and C₁₋₆alkyl.

2. A compound or salt according to Claim 1 wherein R³ is C₃₋₅alkyl.
3. A compound or salt according to Claim 1 or Claim 2 wherein R⁴ is methyl or ethyl.
4. A compound or salt according to any of Claim 1-3 wherein R¹ is pyridinyl and is optionally substituted with a fluorine.

5. A compound or salt according to any of Claims 1-4 wherein Q is C₁₋₆alkyl optionally substituted with 1-3 fluorines.

6. A compound or salt according to any of Claim 1-5 wherein R⁵ is optionally substituted with 1-3 substituents independently selected from F, Cl, and methyl.

7. A compound or salt according to any of Claims 1-6 wherein R² is



wherein R⁶ is methyl; R⁷ is C₂₋₃alkyl, phenyl, OCH₃, CN, or F; and is optionally substituted with 1-2 substituents independently selected from F and CH₃.

8. A pharmaceutical composition comprising a compound or salt according to any of Claims 1-7.

9. The composition of claim 8 further comprising at least one other agent used for treatment of AIDS or HIV infection selected from nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, CAPSID inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors, and a pharmaceutically acceptable carrier.

10. A method for treating HIV infection comprising administering a composition according to Claim 8 to a patient in need thereof.

11. The method of claim 10 further comprising administering at least one other agent used for treatment of AIDS or HIV infection selected from nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, CAPSID inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors.

12. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-7 for use in therapy
13. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-7 for use in treating HIV infection.
14. A compound or pharmaceutically acceptable salt thereof according to any of Claims 1-7 for use in the manufacture of a medicament for the treatment of HIV infection.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/055298

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/14 C07D405/14 C07D491/052 C07D491/107 C07D491/113
A61P31/18 A61K31/4427

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/025915 A1 (VIIV HEALTHCARE UK LTD [GB]) 16 February 2017 (2017-02-16) page 125; example 63 claims	1-14
A,P	----- WO 2018/127800 A1 (VIIV HEALTHCARE UK NO 5 LTD [GB]) 12 July 2018 (2018-07-12) abstract examples claims -----	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 November 2019

Date of mailing of the international search report

09/12/2019

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2019/055298

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			AU 2016306087 A1 08-03-2018
			BR 112018002689 A2 27-11-2018
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			CN 108349939 A 31-07-2018
			EP 3334724 A1 20-06-2018
			JP 2018522926 A 16-08-2018
			KR 20180035914 A 06-04-2018
			RU 2018106504 A 13-09-2019
			TW 201718537 A 01-06-2017
			US 2018230124 A1 16-08-2018
			WO 2017025915 A1 16-02-2017

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			TW 201835068 A 01-10-2018
			UY 37555 A 31-08-2018
			WO 2018127800 A1 12-07-2018
