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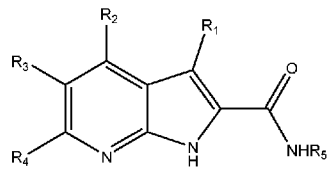
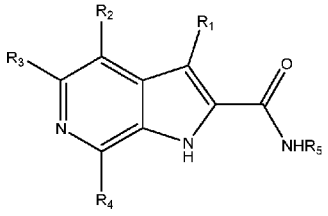
(54) Title: AZAINDOLE CARBOXAMIDE COMPOUNDS FOR THE TREATMENT OF MYCOBACTERIAL INFECTIONS

(57) Abstract: Provided herein are compounds of Formula (I) and Formula (II): as well as pharmaceutically acceptable salts thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of tuberculosis.



(I)



(II),

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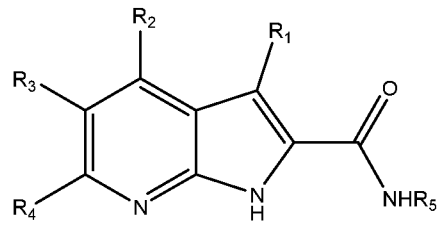
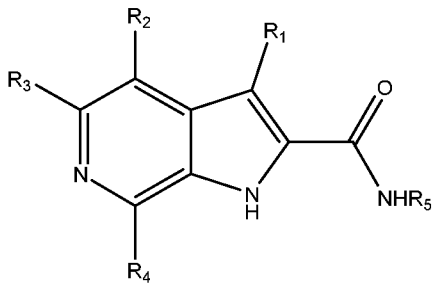
AZAINDOLE CARBOXAMIDE COMPOUNDS FOR THE TREATMENT OF MYCOBACTERIAL INFECTIONS

FIELD OF THE INVENTION

The invention is directed to, for example, compounds of Formula (I) and compounds of Formula (II):



(I)



(II)

and to pharmaceutical compositions comprising the compounds. The compounds and compositions disclosed herein are antibacterials and are useful for the treatment of tuberculosis and other mycobacterial infections.

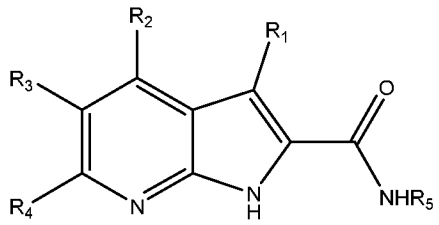
All publications, patents, patent applications, and other references cited in this application are incorporated herein by reference in their entirety for all purposes and to the same extent as if each individual publication, patent, patent application or other reference was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Citation of a reference herein shall not be construed as an admission that such is prior art to the present invention.

BACKGROUND OF THE INVENTION

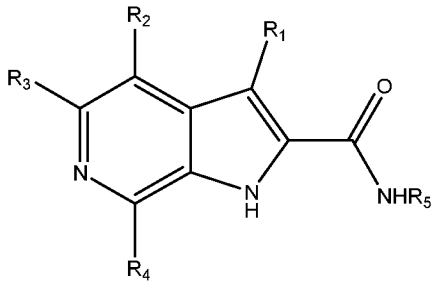
Mycobacterium tuberculosis ("M. tb") is the causative agent of tuberculosis ("TB"), a devastating infectious disease. It is estimated that about 2 million TB patients die each year globally. The treatment of drug-susceptible TB currently centers on four antibiotics, isoniazid, rifampicin, ethambutol, and pyrazinamide which were introduced more than 40 years ago (Franz 2017). Failure to properly treat tuberculosis has caused global drug resistance in Mtb and thus rendering some medications ineffective. A need exists in the art, therefore, to identify new chemical entities to treat TB.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I) and Formula (II):



(I)



(II)

wherein:

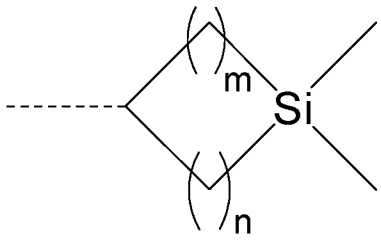
R_1 is hydrogen or lower alkyl;

R_2 is hydrogen, lower alkyl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

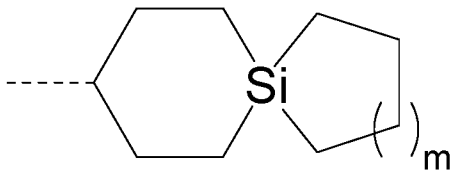
R_3 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

R_4 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, cycloalkoxy, or carboxamide;

R_5 is: lower alkyl, cycloalkyl, cycloalkylene or -CH_2-cycloalkyl, spiral(C_8-C_{11})cycloalkyl, phenyl, a bridged cycloalkyl or



wherein m is 1, 2 or 3 and n is 1, 2, 3, or 4; or



wherein m is 1 or 2;

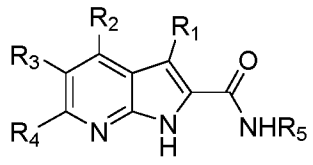
or a pharmaceutically acceptable salt thereof.

The present invention is also directed to pharmaceutical compositions containing the above compounds and to methods of treating microbial infections such as tuberculosis.

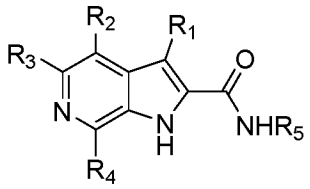
DETAILED DESCIPTION OF THE INVENTION

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, certain methods, devices and materials are now described.

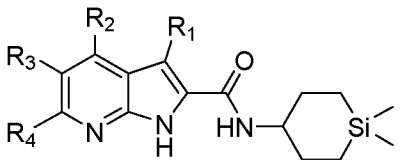
The present invention relates to novel azaindole carboxamide compounds, their preparations, and to their use as drugs for treating tuberculosis and other mycobacteria infections. The compounds, in certain embodiments, have the following general structures:



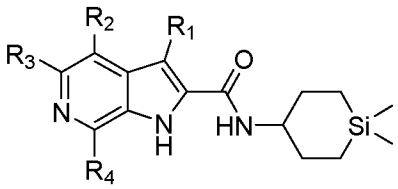
I



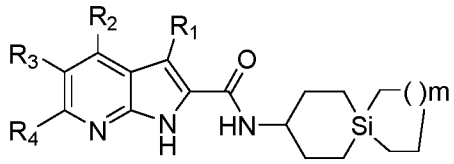
II



III

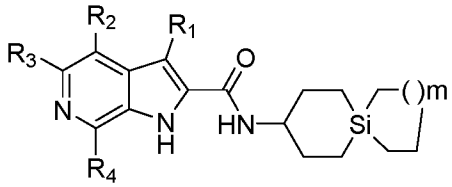


IV



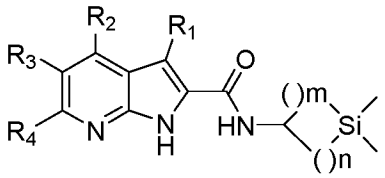
V

m=1, 2



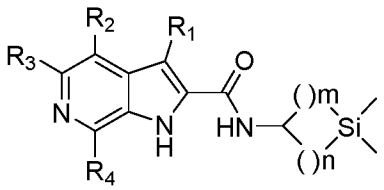
VI

m=1, 2



VII

m=3, n=1-4
m=2, n=1-4
m=1, n=1-4



VIII

m=3, n=1-4
m=2, n=1-4
m=1, n=1-4

In one embodiment of the invention. the compounds of the invention can treat TB in combination with other anti-TB agents. The anti-TB agents include, but are not limited to, rifampicin,

rifabutin, rifapentene, isoniazid, ethambutol, kanamycin, amikacin, capreomycin, clofazimine, cycloserine, para-aminosalicylic acid, linezolid, sutezolid, bedaquiline, delamanid, pretomanid, moxifloxacin, and levofloxacin.

Definitions

As used herein, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, in one embodiment one to sixteen carbon atoms, in another embodiment one to ten carbon atoms.

As used herein, the term "alkenyl", alone or in combination with other groups, refers to a straight-chain or branched hydrocarbon residue having an olefinic bond.

As used herein, the term "alkoxy" means alkyl-O--; and "alkoyl" means alkyl-CO--. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by, for example, one or more alkyl or halo groups.

As used herein, the term "cycloalkoxy" means cycloalkyl-O--. Cycloalkoxy substituent groups may be substituted by, for example, one or more alkyl or halo groups.

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, in some embodiments a fluorine, chlorine or bromine radical.

The term "cycloalkyl" refers to a monovalent mono- or polycarbocyclic radical of three to ten, in one embodiment three to six carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, indanyl and the like. In one embodiment, the "cycloalkyl" moieties can optionally be substituted with one, two, three or four substituents. Each substituent can independently be alkyl, alkoxy, halogen, amino, hydroxyl or oxygen unless otherwise specifically indicated. Examples of cycloalkyl moieties include, but are not limited to, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclopentenyl, optionally substituted cyclohexyl, optionally substituted cyclohexylene, optionally substituted

cycloheptyl, and the like or those which are specifically exemplified herein.

The term "heterocycloalkyl" denotes a mono- or polycyclic alkyl ring, wherein one, two or three of the carbon ring atoms is replaced by a heteroatom such as N, O or S. Examples of heterocycloalkyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrofuranyl, 1,3-dioxanyl and the like. The heterocycloalkyl groups may be unsubstituted or substituted and attachment may be through their carbon frame or through their heteroatom(s) where appropriate.

The term "lower alkyl", alone or in combination with other groups, refers to a branched or straight-chain alkyl radical of one to nine carbon atoms, in one embodiment one to six carbon atoms, in another embodiment one to four carbon atoms, in a further embodiment four to six carbon atoms. This term is further exemplified by radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, isobutyl, t-butyl, n-pentyl, 3-methylbutyl, n-hexyl, 2-ethylbutyl and the like.

The term "aryl" refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, 1H-indenyl and the like.

The alkyl, lower alkyl and aryl groups may be substituted or unsubstituted. When substituted, there will generally be, for example, 1 to 4 substituents present. These substituents may optionally form a ring with the alkyl, lower alkyl or aryl group with which they are connected. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl, in other embodiments, for example, methoxy and ethoxy), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arycarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as

esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylminocarbonloxy) and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more heteroatoms, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

As would be readily understood from the disclosure provided herein, any reference to a group falling within a generic group may be substituted or unsubstituted in the same manner. For example, a phenyl group may be substituted in the same manner as an aryl group.

The term "heteroaryl," refers to an aromatic mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, and S, with the remaining ring atoms being C. Examples of such groups include, but not limited to, pyridinyl, pyrazinyl, pyridazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, oxazolyl, thiazolyl, and the like.

The heteroaryl group described above may be substituted independently with one, two, or three substituents. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arycarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters (e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono- or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, aryloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylminocarbonloxy) and ureas (e.g. mono- or di- alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more heteroatoms, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl, benzothiazoyl and carbolinyl).

In some instances, a term is preceded by "($C_{\#}$ - $C_{\#}$)." As would be readily understood from the disclosure provided herein, this defines the number of carbon atoms associated with the term. For example, (C_1-C_6)alkyl means an alkyl in which the branched or straight-chain monovalent saturated aliphatic hydrocarbon radical has one to 6 carbon atoms. As would be readily understood from the disclosure provided herein, all substitution definitions apply equally to these structures. For example, (C_1-C_6)alkyl may be substituted in the same manner an alkyl is substituted.

By any range disclosed herein, it is meant that all integer unit amounts within the range are specifically disclosed as part of the invention. Thus, for example, 1 to 12 units means that 1, 2, 3 . . . 12 units are included as embodiments of this invention.

Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). The invention embraces all of these forms.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention, or a combination of any of the compounds of this invention, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered, for example, ocularly, orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases. Thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are representative liquid carriers, particularly (when isotonic with the blood) for injectable solutions.

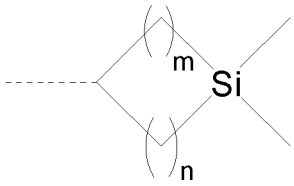
For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution,and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as a "therapeutically effective amount". For example, the dose of a compound of the present invention is typically in the range of about 1 to about 1000 mg per day. In one embodiment, the therapeutically effective amount is in an amount of from about 10 mg to about 500 mg per day.

It will be appreciated that the compounds of the invention may be derivatized at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula I in vivo are also within the scope of this invention.

Compounds of the present invention can be prepared beginning with commercially available starting materials and utilizing general synthetic techniques and procedures known to those skilled in the art. Chemicals may be purchased from companies such, as for example, Aldrich, Argonaut Technologies, VWR and Lancaster. Chromatography supplies and equipment may be

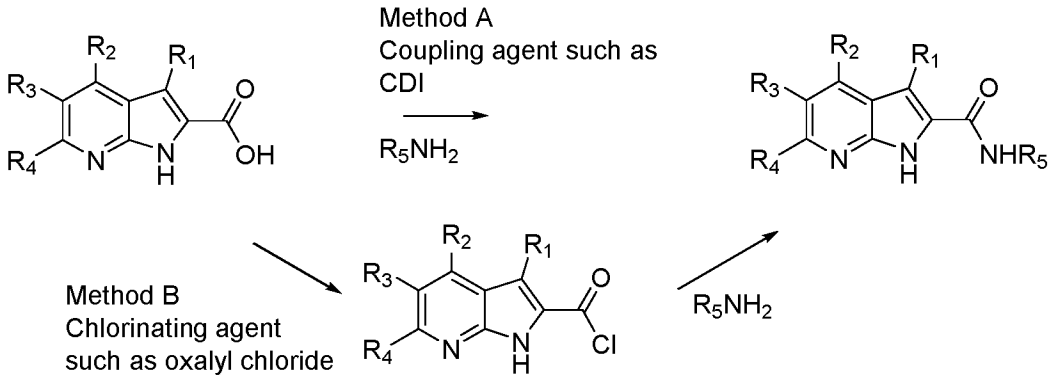
purchased from such companies as for example AnaLogix, Inc, Burlington, Wis.; Biotage AB, Charlottesville, Va.; Analytical Sales and Services, Inc., Pompton Plains, N.J.; Teledyne Isco, Lincoln, Nebr.; VWR International, Bridgeport, N.J.; Varian Inc., Palo Alto, Calif., and Multigram II Mettler Toledo Instrument Newark, Del. Biotage, ISCO and Analogix columns are pre-packed silica gel columns used in standard chromatography.

In some embodiments, R_5 is 

and m is 1-3 and n is 1-4. In another embodiment, m is 1 and n is 1. In another embodiment, m is 1 and n is 2. In another embodiment, m is 1 and n is 3. In another embodiment, m is 1 and n is 4. In another embodiment, m is 2 and n is 1. In another embodiment, m is 2 and n is 2. In another embodiment, m is 2 and n is 3. In another embodiment, m is 2 and n is 4. In another embodiment, m is 3 and n is 1. In another embodiment, m is 3 and n is 2. In another embodiment, m is 3 and n is 3. In another embodiment, m is 3 and n is 4. In the case where m is not eqaul to n, there exists a stereocenter in the amine and in the resulting amide. The product may be a mixture or it may be resolved individual stereoisomers of the amide although the abolute stereochemical assignments are not made. Under such a case, a number (MPL-xxx) without a suffix A or B is meant for a racemic mixture wheras suffix A and B (such as MPL-xxxA and MPL-xxxB) is meant to indicate resolved enantiomers although no absolute configuration has been assigned to each enantiomer. Separation of stereoisomers are most effectively achieved by the use of Super Fluid Chromatography (SFC) equipped with a chiral column.

Synthesis of Representative Compounds of the Invention

The compounds of the invention can be prepared according to the following Scheme showing general methods A and B:



EXAMPLES

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Abbreviations used: ABPR, automatic back-pressure regulator; ACN, acetonitrile; aq., aqueous; 9-BBN, 9-borabicyclo[3.3.1]nonane; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; BMS, borane-dimethyl sulfide; Boc, tert-butoxycarbonyl;

CDI, 1,1'-carbonyl diimidazole; m-CPBA, meta-chloroperbenzoic acid; DABCO: 1,4-diazabicyclo[2.2. 2]octane; DCM, dichloromethane; DEA, diethyl amine; DMAP, 4-dimethylaminopyridine; DME, dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; ESI, electrospray ionization; eq, equivalent; vHMDS, bis(trimethylsilyl)amine; NBS, N-bromosuccinimide; HOBt, hydroxybenzotriazole; HPLC, high performance liquid chromatography; IPA, isopropyl alcohol; LAH, lithium aluminium hydride; LCMS or LC-MS, liquid chromatography–mass spectrometry; LDA, lithium diisopropylamide; min, minute; m/z, mass-to-charge ratio; NCS, N-chlorosuccinimide; NFSI, N-fluorodibenzenesulfonimide; NIS, N-iodosuccinimide; nm,

nanometer; NMP, N-methyl-2-pyrrolidone; NMI, 1-methylimidazole; NMR, nuclear magnetic resonance; ^{1}H NMR, proton NMR; Pd(dppf)Cl2, 1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II); Pd2(dpa)3, tris(dibenzylideneacetone)dipalladium(0); prep-HPLC, preparative HPLC; prep-TLC, preparative TLC; psi, pound per square inch; SFC, supercritical fluid chromatography; TBAF, tetra-n-butylammonium fluoride; TCFH, chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate; TEA, triethylamine; THF, tetrahydrofuran; TLC, Thin-layer chromatography; TIPS, triisopropyl silyl; TIPSCl, triisopropylsilyl chloride; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; TMSCl, chloro(trimethyl)silane; Tos, p-tolylsulfonyl; TosCl, 4-Toluenesulfonyl chloride; ul, microliter; umol, micromole; XantPhos, 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl; δ, chemical shift in ppm.

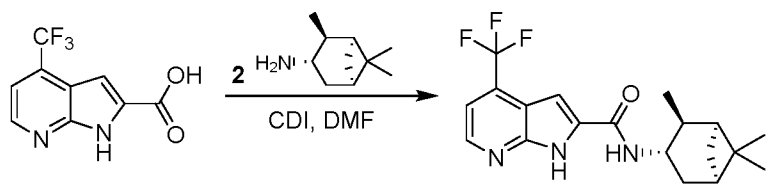
Reactions were monitored by TLC or LCMS and compounds were characterized by LCMS and/or NMR. Shimadzu LC20-MS2010 or LC20-MS2020 were used for LC/MS analysis. Varian 400 MHz, Varian 500 MHz or Bruker 500 MHz were used for NMR measurement.

General conditions for prep-HPLC purification: Instrument: Gilson GX281; Flow rate: 25 mL/min; Detector: UV 220 and UV 254.

"[water (X)-Y]; B%: J%-K%, L min" stands for mobile phase: A: X in water; B: Y; gradient J%-K%B over L min. For example, '[water(0.225%FA)-ACN];B%: 36%-66%,11min' means mobile phase: A: 0.025% formic acid in water, B: acetonitrile; gradient: 36%-66%B over 11 min.

Example 1. MPL-015

Synthesis of 4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



13 MPL-015

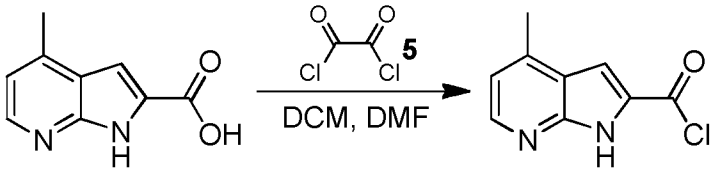
To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (1.5 g, 6.52 mmol, 1 *eq*) in DMF (20 mL) was added CDI (1.59 g, 9.78 mmol, 1.5 *eq*) and stirred at 25 °C for 0.5 h. Then, (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (1.60 g, 10.43 mmol, 1.6 *eq*) was added above solution and stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely and one main peak with desired MS was detected. The mixture was added water (70 mL) and extracted with EtOAc (200 mL x 3) and the organic phase was washed with water (30 mL x 3) and brine (30 mL x 3) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 1/0 to 200/1). Compound 4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (2.07 g, 5.67 mmol, 86.92% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 366.2 $[M+H]^+$

^{1}H NMR (500MHz, DMSO-d_6) δ = 12.78 (s, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 4.9 Hz, 1H), 7.50 (d, *J* = 4.9 Hz, 1H), 7.40 (s, 1H), 4.47 - 4.35 (m, 1H), 2.47 - 2.35 (m, 2H), 2.10 (quin, *J* = 7.1 Hz, 1H), 1.96 (br d, *J* = 2.7 Hz, 1H), 1.83 (t, *J* = 5.4 Hz, 1H), 1.86 - 1.80 (m, 1H), 1.73 (ddd, *J* = 1.8, 6.4, 13.6 Hz, 1H), 1.26 - 1.20 (m, 4H), 1.11 - 1.05 (m, 6H).

Example 2. MPL-016

Synthesis of 4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



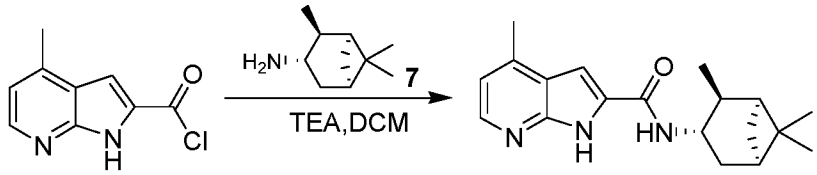
4 **6**

Oxalyl dichloride (1.62 g, 12.77 mmol, 1.12 mL, 15 *eq*) was added to the solution of 4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (150 mg, 851.44 umol, 1 *eq*) in DCM (8.0 mL). Then, 3 drops of DMF (3.11 mg, 42.57 umol, 3.28 uL, 0.05 *eq*) was added above solution and

stirred at 25 °C for 2 hrs. LCMS showed the starting material consumed completely and the desired MS was detected. The residue was concentrated under reduced pressure to give a residue was added DCM (25 mL x 3) and concentrated under reduced pressure to give a compound 4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (160 mg, crude) as a yellow solid

LCMS (ESI) m/z: 190.9 $[M+H]^+$;

Synthesis of 4-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



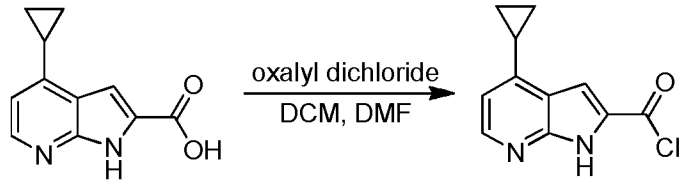
6 **MPL-016**

4-Methyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (160 mg, 822.13 umol, 0.91 *eq*) was added to the solution of (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (138.46 mg, 903.44 umol, 1 *eq*) and TEA (365.68 mg, 3.61 mmol, 502.99 uL, 4.0 *eq*) in DCM (10 mL) and stirred at 25 °C for 2.0 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (20 mL) and extracted with DCM (30 mL x 3). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 14:1) Compound 4-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2- carboxamide (15 mg, 48.17 umol, 5.33% yield, 100% purity) was obtained as yellow solid. LCMS (ESI) m/z: 312.2 $[M+H]^+$;

1H NMR (400MHz, DMSO-d6) δ =11.96 (br s, 1H), 8.33 (br d, *J*=8.4 Hz, 1H), 8.17 (d, *J*=4.6 Hz, 1H), 7.21 (s, 1H), 6.91 (d, *J*=4.6 Hz, 1H), 4.43 - 4.25 (m, 1H), 2.51 (s, 3H), 2.45 - 2.29 (m, 2H), 2.05 (quin, *J*=7.0 Hz, 1H), 1.93 (br s, 1H), 1.80 (br t, *J*=5.2 Hz, 1H), 1.71 - 1.63 (m, 1H), 1.21 (s, 3H), 1.17 (br d, *J*=9.5 Hz, 1H), 1.07 - 1.00 (m, 6H).

Example 3. MPL-017

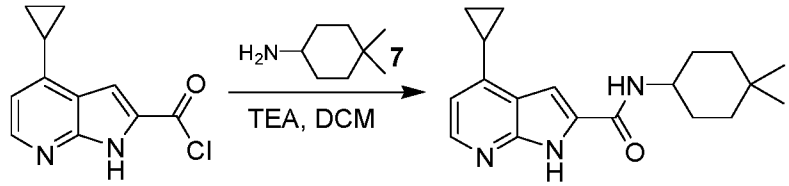
Synthesis of 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



5 **6**

Oxalyl dichloride (3.77 g, 29.67 mmol, 2.60 mL, 40 *eq*) was added to the solution of 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (150 mg, 741.81 umol, 1 *eq*) in DCM (10 mL). Then, 3 drops of DMF (2.71 mg, 37.09 umol, 2.85 uL, 0.05 *eq*) was added above solution and stirred at 25 °C for 2.0 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The residue was concentrated under reduced pressure to give a residue was added DCM (25 mL x 3) and concentrated under reduced pressure to give a compound 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (160 mg, crude) as a yellow solid. LCMS (ESI) m/z: 217 $[M+H]^+$;

Synthesis of 4-cyclopropyl-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



6 **MPL-017**

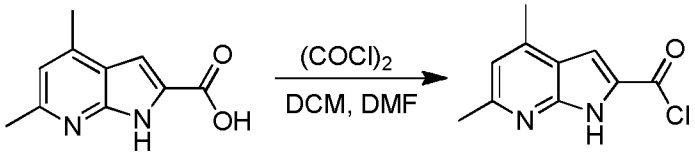
4,4-Dimethylcyclohexanamine (90 mg, 707.40 umol, 1 *eq*) was added to the solution of 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (160 mg, 725.12 umol, 1.03 *eq*) in DCM (10 mL). Then, TEA (214.75 mg, 2.12 mmol, 295.39 uL, 3.0 *eq*) was added above solution and stirred at 25 °C for 12 hrs. LCMS showed the desired MS was detected. The mixture was added water (15 mL) and extracted with DCM (50 mL x 3) and the organic phase was dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 50:1).

Compound 4-cyclopropyl-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (44.4 mg, 139.84 umol, 19.77% yield, 98.086% purity) was obtained as a white solid. LCMS (ESI) m/z: 312.2 $[M+H]^+$;

^1H NMR (400MHz, DMSO-d6) δ =13.01 (br s, 1H), 8.61 (br d, *J*=7.9 Hz, 1H), 8.25 (d, *J*=5.7 Hz, 1H), 7.55 (s, 1H), 6.94 (d, *J*=6.0 Hz, 1H), 3.78 - 3.64 (m, 1H), 2.44 - 2.35 (m, 1H), 1.71 - 1.63 (m, 2H), 1.59 - 1.48 (m, 2H), 1.44 - 1.36 (m, 2H), 1.36 - 1.24 (m, 4H), 1.18 - 1.13 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H).

Example 4. MPL-019

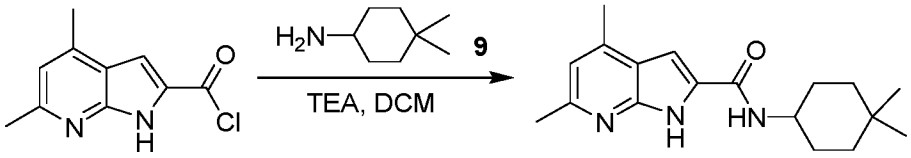
Synthesis of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



7 **8**

Oxalyl dichloride (8.70 g, 68.54 mmol, 6.0 mL, 128.28 *eq*) was added to the solution of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 525.77 umol, 1 *eq*) in DCM (6.0 mL). Then, 3 drops of DMF (1.92 mg, 26.29 umol, 2.02 uL, 0.05 *eq*) was added above solution and stirred at 25 °C for 1.5 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The residue was concentrated under reduced pressure to give a residue was added DCM (25 mL x 3) and concentrated under reduced pressure to give a compound 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, crude) as a yellow solid. LCMS (ESI) m/z: 205.1 $[M+H]^+$;

Synthesis of N-(4,4-dimethylcyclohexyl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



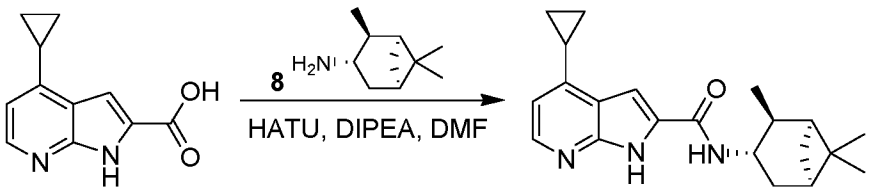
8 MPL-019

To a solution of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, 479.29 umol, 1 *eq*) and 4,4-dimethylcyclohexanamine (121.96 mg, 958.57 umol, 2.0 *eq*) in DCM (10 mL) was added TEA (145.50 mg, 1.44 mmol, 200.13 uL, 3.0 *eq*). The mixture was stirred at 25 °C for 0.5 hr. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 150:1). Compound N-(4,4-dimethylcyclohexyl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (64.7 mg, 186.68 umol, 38.95% yield, 99.671% purity, FA) was obtained as a white solid. LCMS (ESI) m/z: 300.2 $[M+H]^+$;

^{1}H NMR (400MHz, DMSO-d6) δ =11.57 (br s, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 8.12 (s, 1H), 7.10 (s, 1H), 6.85 (s, 1H), 3.81 - 3.66 (m, 1H), 2.47 - 2.46 (m, 3H), 2.45 (s, 3H), 1.70 - 1.63 (m, 2H), 1.59 - 1.47 (m, 2H), 1.43 - 1.36 (m, 2H), 1.32 - 1.23 (m, 2H), 0.92 (d, *J*=10.4 Hz, 6H)

Example 5. MPL-022

Synthesis of 4-cyclopropyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



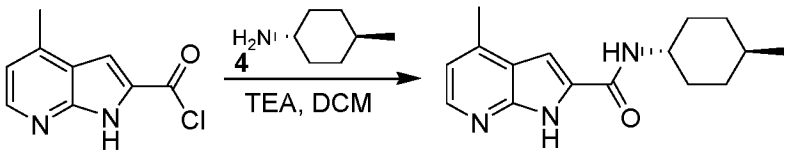
7 MPL-022

To a solution of 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 989.08 umol, 1 *eq*) in DMF (10 mL) was added HATU (451.29 mg, 1.19 mmol, 1.2 *eq*), DIEA (383.49 mg, 2.97 mmol, 516.84 uL, 3.0 *eq*) and (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (166.75

mg, 1.09 mmol, 1.1 *eq*). The reaction was stirred at 25 °C for 3.0 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added to water (40 mL), extracted with EtOAc (50 x 3 mL). The organic phase was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 36%-66%,11min). Compound 4-cyclopropyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (16 mg, 47.41 umol, 4.79% yield, 100% purity) was obtained as a light brown solid. LCMS (ESI) m/z: 338.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.03 (br s, 1H), 8.34 (d, *J*=8.4 Hz, 1H), 8.14 (d, *J*=5.1 Hz, 1H), 7.31 (s, 1H), 6.68 (d, *J*=5.1 Hz, 1H), 4.36 (quin, *J*=8.0 Hz, 1H), 2.46 - 2.33 (m, 2H), 2.29 - 2.21 (m, 1H), 2.10 - 2.00 (m, 1H), 1.94 (br s, 1H), 1.83 - 1.78 (m, 1H), 1.72 - 1.63 (m, 1H), 1.22 (s, 3H), 1.19 - 1.11 (m, 3H), 1.05 (t, *J*=3.5 Hz, 6H), 1.01 - 0.95 (m, 2H).

Example 6. MPL-029

Synthesis of 4-methyl-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



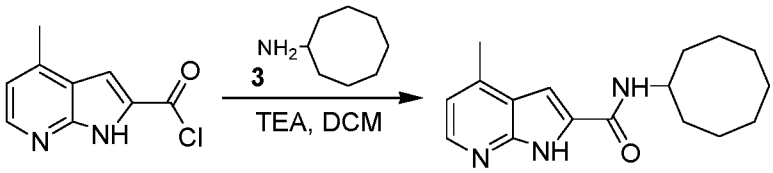
3 **MPL-029**

4-Methylcyclohexanamine (70 mg, 618.37 umol, 1 *eq*) was added to the solution of 4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (110 mg, 565.21 umol, 9.14e-1 *eq*) in DCM (8.0 mL). Then, TEA (187.72 mg, 1.86 mmol, 258.21 uL, 3.0 *eq*) was added above solution and stirred at 25 °C for 2.0 hrs. LCMS showed the starting material was consumed completely. The mixture was added water (15 mL) and extracted with DCM (50 mL x 3). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 50:1). Compound 4-methyl-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (57 mg, 210.06 umol, 33.97% yield, 100% purity) was obtained as a yellow solid.

LCMS (ESI) m/z: 272.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.65 (br s, 1H), 8.46 (br d, *J*=8.2 Hz, 1H), 8.27 (br s, 1H), 7.36 (s, 1H), 7.14 (br d, *J*=4.0 Hz, 1H), 3.80 - 3.60 (m, 1H), 2.60 (s, 3H), 1.84 (br d, *J*=10.6 Hz, 2H), 1.69 (br d, *J*=12.3 Hz, 2H), 1.41 - 1.27 (m, 3H), 1.08 - 0.94 (m, 2H), 0.87 (d, *J*=6.4 Hz, 3H).

Example 7. MPL-031

Synthesis of N-cyclooctyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



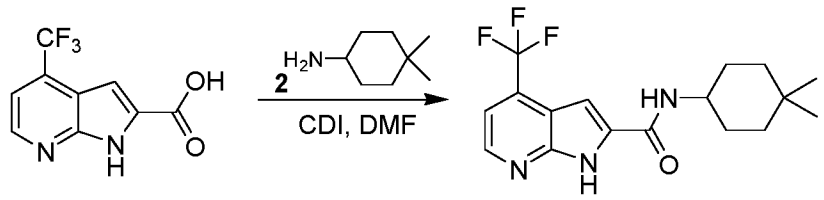
2 **MPL-031**

4-Methyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (130mg, 667.98 umol, 0.91 *eq*) was added to the solution of cyclooctanamine (100 mg, 786.00 umol, 1.07 *eq*) and TEA (222.83 mg, 2.20 mmol, 306.51 uL, 3.0 *eq*) in DCM (8.0 mL) and stirred at 25 °C for 2.0 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 90:1). Then, the residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 35%-55%,11min). Compound N-cyclooctyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (27.3 mg, 95.66 umol, 13.03% yield, 100% purity) was obtained as a light brown solid.

LCMS (ESI) m/z: 286.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.99 (br s, 1H), 8.28 - 8.10 (m, 2H), 7.22 (s, 1H), 6.94 (br s, 1H), 4.09 - 3.96 (m, 1H), 2.52 (br s, 3H), 1.83 - 1.66 (m, 6H), 1.62 - 1.47 (m, 8H).

Example 8. MPL-010

Synthesis of N-(4,4-dimethylcyclohexyl)-4-(trifluoromethyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



1 MPL-010

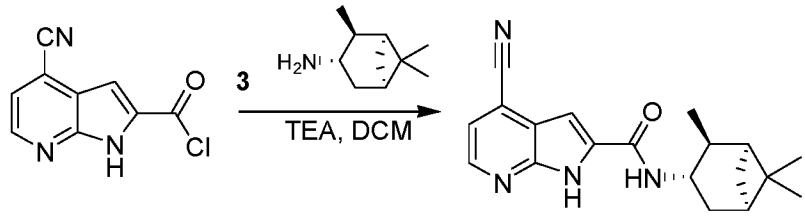
To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (80 mg, 347.61 umol, 1 *eq*) in DMF (5.0 mL) was added CDI (73.27 mg, 451.89 umol, 1.3 *eq*) and stirred at 25 °C for 15 min. Then, 4,4-dimethylcyclohexanamine (66.34 mg, 521.41 umol, 1.5 *eq*) was added above solution and stirred at 25 °C for 12 hrs. LCMS showed the starting material was consumed completely and one main peak with desired MS was detected. The mixture was diluted with DCM (20 mL) and washed with water (20 mL x 5) and HCl (1M, 20mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 80:1). Compound N-(4,4-dimethylcyclohexyl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (30.1 mg, 87.99 umol, 25.31% yield, 99.203% purity) was obtained as a white solid.

LCMS (ESI) m/z: 340.1 $[M+H]^+$;

^{1}H NMR (400MHz, DMSO-d6) δ = 12.71 (br s, 1H), 8.56 - 8.42 (m, 2H), 7.46 (d, *J*=4.9 Hz, 1H), 7.33 (d, *J*=1.2 Hz, 1H), 3.82 - 3.62 (m, 1H), 1.70 - 1.61 (m, 2H), 1.59 - 1.45 (m, 2H), 1.43 - 1.34 (m, 2H), 1.33 - 1.21 (m, 2H), 0.92 (d, *J*=9.3 Hz, 6H).

Example 9. MPL-013

Synthesis of 4-cyano-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

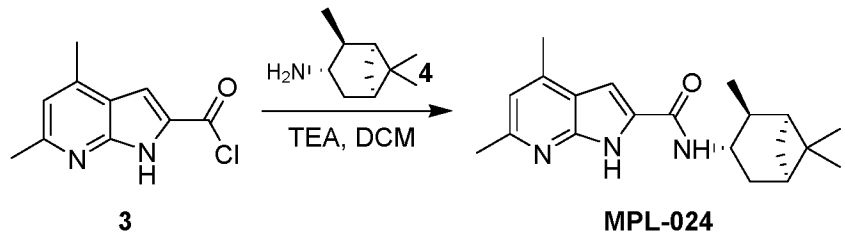


To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, 486.38 umol, 1.0 *eq*) and (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (149.09 mg, 972.76 umol, 2.0 *eq*) in DCM (10 mL) was added TEA (147.65 mg, 1.46 mmol, 203.10 uL, 3.0 *eq*). The mixture was stirred at 25 °C for 0.5 hr. LCMS showed the starting material was consumed completely and the desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 200:1). Compound 4-cyano-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (87.3 mg, 270.78 umol, 55.67% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 323.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ=12.86 (s, 1H), 8.63 (br d, *J*=8.6 Hz, 1H), 8.52 (d, *J*=4.9 Hz, 1H), 7.64 (d, *J*=4.9 Hz, 1H), 7.48 (s, 1H), 4.46 - 4.32 (m, 1H), 2.47 - 2.32 (m, 2H), 2.09 (quin, *J*=7.4 Hz, 1H), 1.99 - 1.92 (m, 1H), 1.85 - 1.79 (m, 1H), 1.76 - 1.67 (m, 1H), 1.24 (s, 3H), 1.20 (d, *J*=9.5 Hz, 1H), 1.07 (t, *J*=3.5 Hz, 6H).

Example 10. MPL-024

Synthesis of 4,6-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide



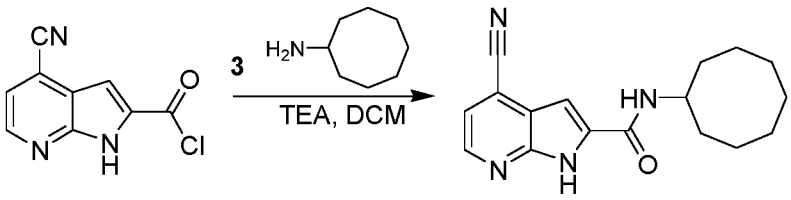
To a solution of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, 479.29 umol, 1 *eq*) and (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (146.91 mg, 958.57 umol, 2.0

eq) in DCM (10 mL) was added TEA (145.50 mg, 1.44 mmol, 200.13 uL, 3.0 *eq*). The mixture was stirred at 25 °C for 1.0 hr. LCMS showed the starting material was consumed completely and the desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 170:1). Compound 4,6-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (84 mg, 257.77 umol, 53.78% yield, 99.87% purity) was obtained as a white solid.

LCMS (ESI) m/z: 326.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.55 (s, 1H), 11.62 - 11.50 (m, 1H), 8.36 (br d, *J*=8.6 Hz, 1H), 7.13 (d, *J*=2.0 Hz, 1H), 6.85 (s, 1H), 4.48 - 4.28 (m, 1H), 2.47 - 2.46 (m, 3H), 2.45 (s, 3H), 2.43 - 2.26 (m, 2H), 2.12 - 2.02 (m, 1H), 1.93 (br s, 1H), 1.80 (br t, *J*=5.2 Hz, 1H), 1.75 - 1.65 (m, 1H), 1.24 - 1.19 (m, 4H), 1.08 - 1.02 (m, 6H).

Example 11. MPL-036

Synthesis of 4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



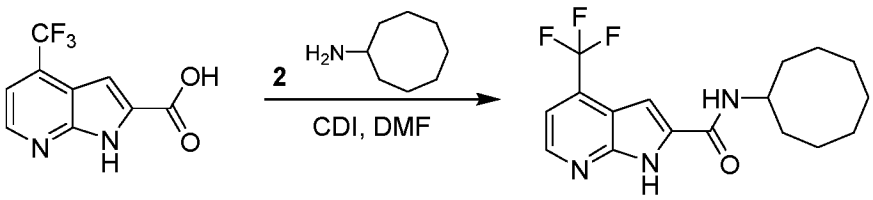
2 **MPL-036**

To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, 486.38 umol, 1.0 *eq*) and cyclooctanamine (123.76 mg, 972.76 umol, 2.0 *eq*) in DCM (10 mL) was added TEA (147.65 mg, 1.46 mmol, 203.10 uL, 3.0 *eq*). The mixture was stirred at 25 °C for 0.5 hr. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: DAICEL CHIRALPAK AS-H(250mm*30mm,5um);mobile phase: [0.1%NH3H2O ETOH];B%: 25%-25%,min) from SFC. Compound 4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (10 mg, 33.74 umol, 6.94% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 297.2 [M+H]+; 1H NMR (400MHz, DMSO-d6) δ =12.80 (br s, 1H), 8.55 - 8.43 (m, 2H), 7.60 (br d, *J*=4.6 Hz, 1H), 7.42 (s, 1H), 4.03 (br s, 1H), 1.81 - 1.43 (m, 14H).

Example 12. MPL-037

Synthesis of N-cyclooctyl-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



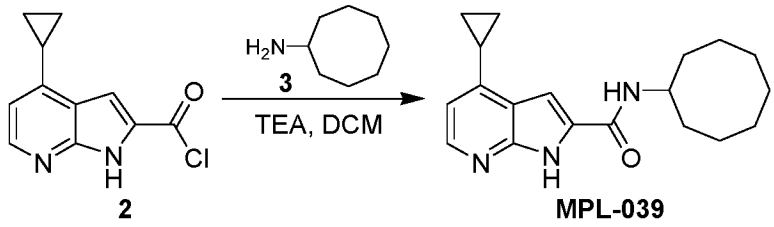
1 **MPL-037**

To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 869.02 umol, 1 *eq*) in DMF (4.5 mL) was added CDI (183.18 mg, 1.13 mmol, 1.3 *eq*) and stirred at 25 °C for 15 min. Then, cyclooctanamine (176.90 mg, 1.39 mmol, 1.6 *eq*) was added above solution and stirred at 25 °C for 12 h. LCMS showed one main peak with desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3) and the organic phase was washed with water (10 mL x 3) and brine (10 mL x 3) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 1/0 to 160:1). Compound N-cyclooctyl-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (212.3 mg, 622.08 umol, 71.58% yield, 99.437% purity) was obtained as a white solid.

LCMS (ESI) m/z: 340.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.73 (br s, 1H), 8.62 - 8.44 (m, 2H), 7.47 (d, *J* = 4.7 Hz, 1H), 7.37 (s, 1H), 4.06 (br dd, *J* = 3.8, 8.1 Hz, 1H), 1.85 - 1.64 (m, 6H), 1.63 - 1.46 (m, 8H).

Example 13 MPL-039

Synthesis of N-cyclooctyl-4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

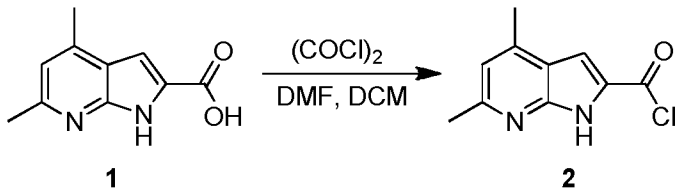


Cyclooctanamine (100 mg, 786.00 umol, 1 *eq*) was added to the solution of 4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (160 mg, 725.12 umol, $9.23e^{-1}$ *eq*) in DCM (10 mL). Then, TEA (238.61 mg, 2.36 mmol, 328.21 uL, 3.0 *eq*) was added above solution and stirred at 25 °C for 2.0 hrs. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 80:1). Compound N-cyclooctyl-4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (106.1 mg, 333.83 umol, 42.47% yield, 97.984% purity) was obtained as a light brown solid.

LCMS (ESI) m/z: 312.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ =13.10 (br s, 1H), 8.66 (br d, *J*=7.9 Hz, 1H), 8.26 (d, *J*=6.0 Hz, 1H), 7.59 (s, 1H), 6.95 (d, *J*=6.0 Hz, 1H), 4.09 - 3.94 (m, 1H), 2.45 - 2.37 (m, 1H), 1.81 - 1.62 (m, 6H), 1.52 (br t, *J*=10.9 Hz, 8H), 1.38 - 1.28 (m, 2H), 1.20 - 1.13 (m, 2H).

Example 14. MPL-041

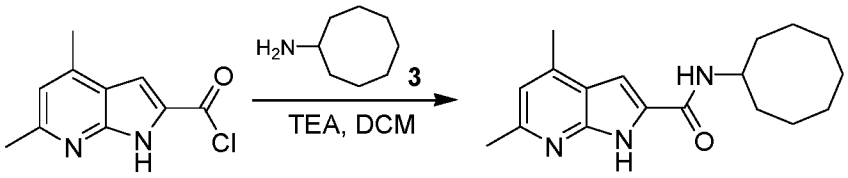
Synthesis of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



Oxalyl dichloride (8.70 g, 68.54 mmol, 6.0 mL, 128.28 *eq*) was added to the solution of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 525.77 umol, 1 *eq*) in DCM (6.0

mL). Then, 3 drops of DMF (1.92 mg, 26.29 umol, 2.02 uL, 0.05 *eq*) was added above solution and stirred at 25 °C for 1.5 hrs. LCMS showed the starting material was consumed completely and the desired mass was detected. The residue was concentrated under reduced pressure to give a residue was added DCM (25 mL 3 3) and concentrated under reduced pressure to give a compound 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, crude) as a yellow solid. LCMS (ESI) m/z: 205.0 $[M+H]^+$;

Synthesis of N-cyclooctyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



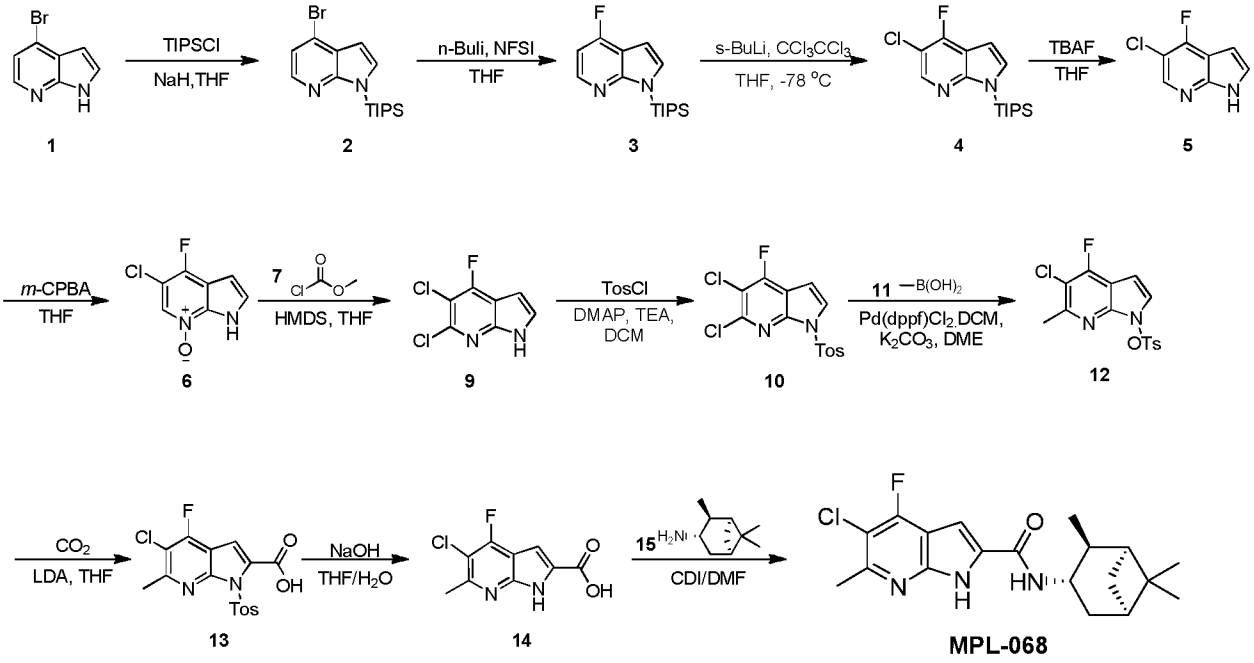
2 **MPL-041**

To a solution of 4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (100 mg, 479.29 umol, 1 *eq*) and cyclooctanamine (121.96 mg, 958.57 umol, 2.0 *eq*) in DCM (10. mL) was added TEA (145.50 mg, 1.44 mmol, 200.13 uL, 3.0 *eq*). The mixture was stirred at 25 °C for 0.5 hr. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1/0 to 150:1). Compound N-cyclooctyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (114.7 mg, 330.72 umol, 69.00% yield, 99.602% purity, FA) was obtained as a white solid.

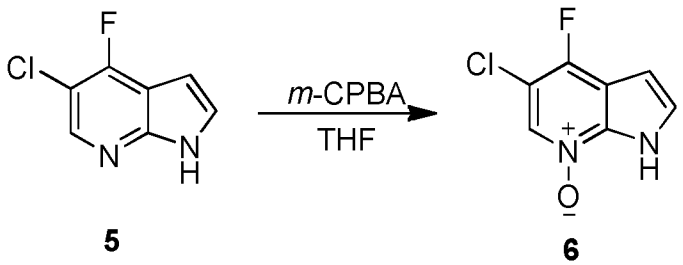
LCMS (ESI) m/z: 300.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ =11.54 (br s, 1H), 8.27 (d, *J*=7.9 Hz, 1H), 8.13 (s, 1H), 7.11 (s, 1H), 6.85 (s, 1H), 4.10 - 3.95 (m, 1H), 2.47 - 2.46 (m, 3H), 2.45 (s, 3H), 1.80 - 1.47 (m, 14H) .

Example 15. MPL-068

Scheme

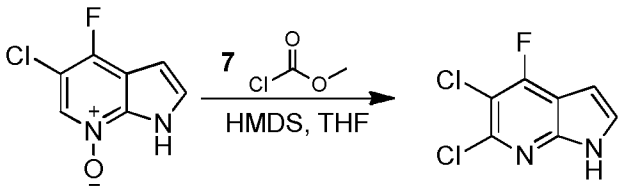


Synthesis of 5-chloro-4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium



To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (4.4 g, 25.80 mmol, 1 *eq*) in DCM (50 mL) was added *m*-CPBA (12.94 g, 63.74 mmol, 85% purity, 2.47 *eq*) at 0 °C. The mixture was stirred at 30°C for 12 hr. LCMS showed the reactant 5 was consumed completely. The sat. Na_2SO_3 (100ml) was added to the mixture and the reaction mixture was stirred for 0.5 h. Then filtered and the inorganic phase was extracted with DCM (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The crude product was used directly for the next step without purification. The crude product 5-chloro-4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (12 g, 22.51 mmol, 87.27% yield, 35% purity) was obtained as brown solid.

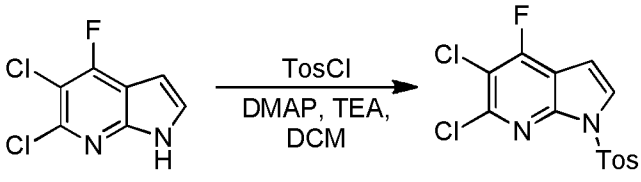
Synthesis of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine



6 9

To a solution of 5-chloro-4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (11 g, 20.64 mmol, 1 *eq*) and HMDS (3.33 g, 20.64 mmol, 4.33 mL, 1 *eq*) in THF (110 mL) was added dropwise methyl carbonochloridate (4.88 g, 51.59 mmol, 4.00 mL, 2.5 *eq*) under N_2, the mixture was stirred at 30 °C for 24 h. LC-MS showed the desired MS was detected. The solvent was removed under reduced pressure and diluted with EtOAc (200 mL). Then the mixture was washed with sat. $NaHCO_3$ (10 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/EtOAc=1:0 to 5:1). The crude product 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (2.4 g, 9.95 mmol, 48.22% yield, 85% purity) as white solid was obtained.

Synthesis of 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

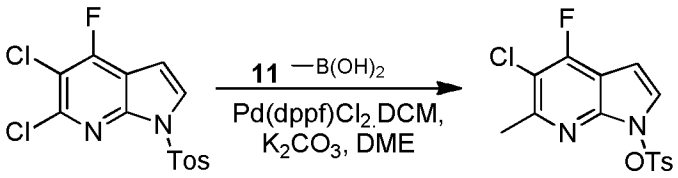


9 10

To a solution of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (580 mg, 2.83 mmol, 1 *eq*) and NaH (565.75 mg, 14.15 mmol, 60% purity, 5 *eq*) in THF (8 mL) was added TosCl (1.08 g, 5.66 mmol, 2 *eq*) under N_2. The mixture was stirred at 25 °C for 12 h. TLC and LCMS showed the desired MS was detected. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (50 mL) at 0 °C, and then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography

(SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 1 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (600 mg, 1.67 mmol, 59.04% yield) was obtained as white solid.

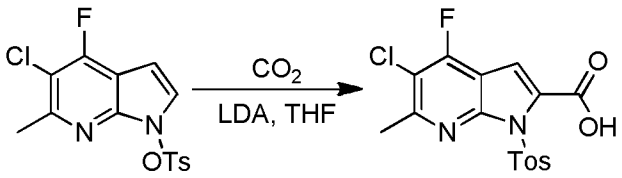
Synthesis of 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



10 **12**

To a solution of methylboronic acid (1.09 g, 18.23 mmol, 5 *eq*) in DME (6 mL) and H2O (0.6 mL) was added 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.31 g, 3.65 mmol, 1 *eq*) $Pd(dppf)Cl_2.CH_2Cl_2$ (297.83 mg, 364.70 umol, 0.1 *eq*) and Na_2CO_3 (1.16 g, 10.94 mmol, 3 *eq*). The mixture was stirred at 120 °C for 12 hr. TLC and LCMS showed the desired MS was detected and the reactant **10** was consumed. The mixture was concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine (680 mg, 2.01 mmol, 55.04% yield, 100% purity) was obtained as white solid.

Synthesis of 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid

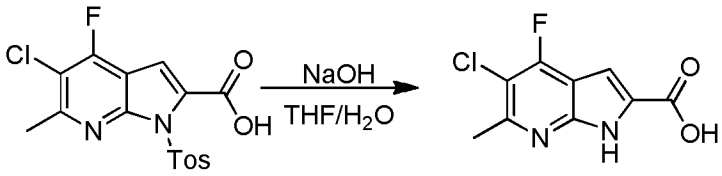


12 **13**

To a solution of CO2 (88.33 mg, 2.01 mmol, 1 *eq*) in THF (8 mL) was added LDA (2 M, 1.51 mL, 1.5 *eq*), the mixture was stirred at -78 °C for 1h under N_2, then 5-chloro-4-fluoro-6-methyl-

1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (680 mg, 2.01 mmol, 1 *eq*) was added and the mixture was stirred at the same temperture for 0.5 h. LCMS showed the desired MS was detected. The reaction was quenched at – 78 °C with saturated aqueous NH_4Cl (30 mL) concentrated under reduced pressure to remove the THF. Then acidified with HCl (2 M) to pH = 5. Then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. After concentration, the crude product was used directly for the next step without purification. The crude product 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine-2-carboxylic acid (700 mg, 1.83 mmol, 91.11% yield) was obtained as brown solid. LCMS (ESI) m/z 382.9 $[M+H]^+$

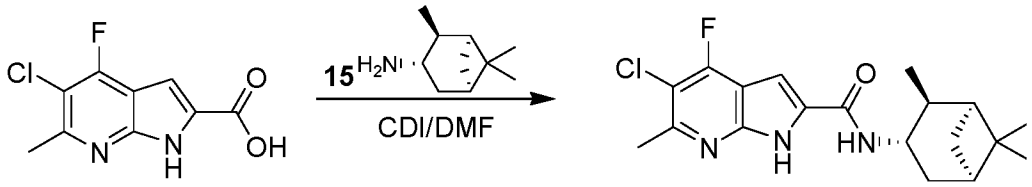
Synthesis of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



13 **14**

To a solution of 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (700 mg, 1.83 mmol, 1 *eq*) in THF (4 mL) was added NaOH (2 M, 4.57 mL, 5 *eq*) (in water), the mixture was stirred at 75 °C for 3 hr. LC-MS showed the starting material 13 was consumed completely. The mixture was concentrated under reduced pressure to give a residue, then diluted with water (10 mL), acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give the crude product. The crude product was purified by washing with EtOAc (5 mL). The product 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 437.43 umol, 23.92% yield, 50% purity) was obtained as a brown solid. LCMS (ESI) m/z 228.9 $[M+H]^+$

Synthesis of 5-chloro-4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan -3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



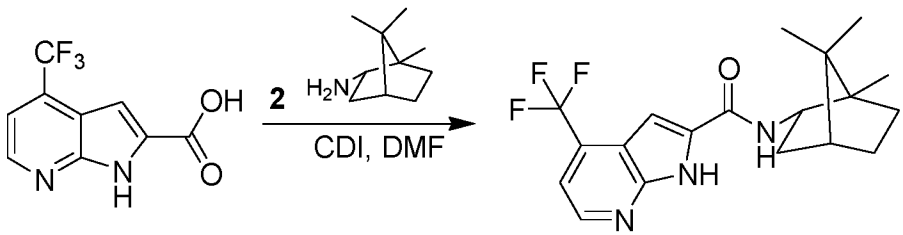
14 MPL-068

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (80 mg, 349.95 umol, 1 *eq*) in DMF (1 mL) was added CDI (85.12 mg, 524.92 umol, 1.5 *eq*), the mixture was stirred at 25 °Cfor 0.5 h, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (80.45 mg, 524.92 umol, 1.5 *eq*) was added , the mixture was stirred at 25 °C for 0.5 h. LCMS showed the reaction was consumed and the desired MS was detected. The residue was purified by Prep--HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 60%-82%,11min) without workup. The product 5-chloro-4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (4.7 mg, 12.19 umol, 3.48% yield, 94.392% purity) was obtained as white solid.

LCMS (ESI) m/z 364.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.50 (br s, 1H), 8.44 (d, *J*=8.4 Hz, 1H), 7.26 (d, *J*=2.1 Hz, 1H), 4.35 (br t, *J*=8.5 Hz, 1H), 2.62 (s, 3H), 2.47 - 2.37 (m, 2H), 2.06 (quin, *J*=6.9 Hz, 1H), 1.94 (br s, 1H), 1.81 (br t, *J*=5.2 Hz, 1H), 1.69 (ddd, *J*=2.1, 6.4, 13.7 Hz, 1H), 1.23 (s, 3H), 1.18 (d, *J*=9.5 Hz, 1H), 1.07 - 1.04 (m, 6H).

Example 16. MPL-108

Synthesis of 4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



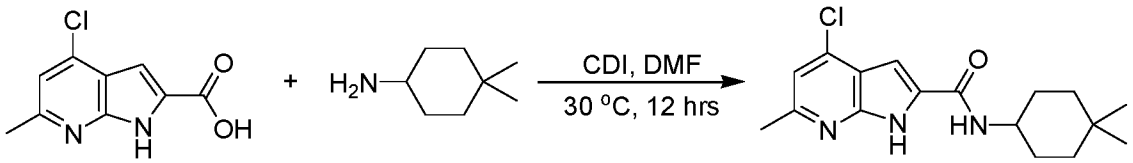
1 MPL-108

To a solution of 4-(trifluoromethyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid (100 mg, 434.51 umol, 1 *eq*) in DMF (3.0 mL) was added CDI (105.68 mg, 651.77 umol, 1.5 *eq*) and stirred at 25 °C for 15 min. Then, 1,7,7-trimethylnorbornan-2-amine (113.21 mg, 738.67 umol, 1.7 *eq*) was added above solution and stirred at 25 °C for 12 h. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3) and the organic phase was washed with water (10 mL x 3) and brine (10 mL x 3) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM/MeOH = 1/0 to 200/1). Compound 4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide (141.2 mg, 382.38 umol, 88.00% yield, 98.952% purity) was obtained as a white solid. LCMS (ESI) m/z: 366.2 $[M+H]^+$

^{1}H NMR (500MHz, DMSO-d_6) δ = 12.77 (br s, 1H), 8.57 (d, *J* = 4.9 Hz, 1H), 8.32 (br d, *J* = 8.5 Hz, 1H), 7.55 - 7.43 (m, 2H), 4.43 (br s, 1H), 2.28 - 2.16 (m, 1H), 1.83 - 1.67 (m, 3H), 1.47 - 1.39 (m, 1H), 1.29 (br t, *J* = 12.1 Hz, 1H), 1.18 (dd, *J* = 4.9, 13.0 Hz, 1H), 1.02 - 0.95 (m, 3H), 0.88 (s, 3H), 0.80 (s, 3H).

Example 17. MPL-119

Synthesis of 4-chloro-N-(4,4-dimethylcyclohexyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



1 **2** **MPL-119**

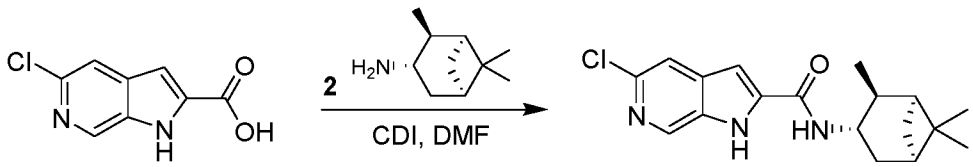
To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (75 mg, 356.10 umol, 1 *eq*) in DMF (2.5 mL) was added CDI (92.39 mg, 569.75 umol, 1.6 *eq*) and stirred at 30 °C for 1 hr. Then, 4,4-dimethylcyclohexanamine (58.90 mg, 462.93 umol, 1.3 *eq*) was added above solution and stirred at 30 °C for 11 hr. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with water (10 mL x 3),

brine (10 mL x 3), dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 300:1). Compound 4-chloro-N-(4,4-dimethylcyclohexyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (58.1 mg, 181.50 umol, 50.97% yield, 99.913% purity) was obtained as a white solid.

LCMS m/z: 320.1 $[M+1]^+$; ^1H NMR (400 MHz, MeOD) δ = 12.29 (s, 1H), 8.34 (br d, *J* = 7.8 Hz, 1H), 7.23 - 7.15 (m, 2H), 3.79 - 3.66 (m, 1H), 2.54 (s, 3H), 1.67 (br dd, *J* = 3.2, 12.8 Hz, 2H), 1.59 - 1.49 (m, 2H), 1.42 (br d, *J* = 12.8 Hz, 2H), 1.28 (dt, *J* = 3.2, 13.1 Hz, 2H), 0.96 (s, 3H), 0.93 (s, 3H).

Example 18. MPL-126

Synthesis of 5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



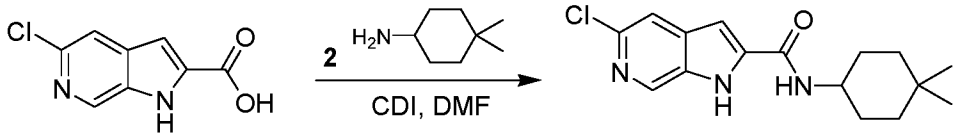
1 MPL-126

To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (80 mg, 406.94 umol, 1 *eq*) in DMF (2.0 mL) was added CDI (92.38 mg, 569.71 umol, 1.4 *eq*) and stirred at 30 °C for 1h. Then, (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (106.03 mg, 691.79 umol, 1.7 *eq*) was added above solution and stirred at 30 °C for 2h. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL x 3), dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 200:1). Compound 5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (62.4 mg, 187.50 umol, 46.08% yield, 99.713% purity) was obtained as a white solid. LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ =12.26 (s, 1H), 8.67 (br d, *J*=8.4 Hz, 1H), 8.58 (s, 1H), 7.78 (s, 1H), 7.25 (s, 1H), 4.40 (td, *J*=7.9, 16.4 Hz,

1H), 2.47 - 2.34 (m, 2H), 2.10 (quin, *J*=6.9 Hz, 1H), 1.96 (br s, 1H), 1.82 (br t, *J*=5.6 Hz, 1H), 1.72 (br dd, *J*=6.4, 12.2 Hz, 1H), 1.26 - 1.19 (m, 4H), 1.10 - 1.03 (m, 6H).

Example 19. MPL-127

Synthesis of 5-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



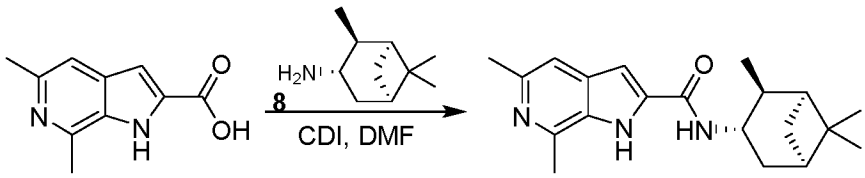
1 **MPL-127**

To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (80 mg, 406.94 umol, 1 *eq*) in DMF (2.0 mL) was added CDI (92.38 mg, 569.71 umol, 1.4 *eq*) and stirred at 30 °C for 1 h. Then, 4,4-dimethylcyclohexanamine (88.01 mg, 691.79 umol, 1.7 *eq*) was added above solution and stirred at 30 °C for 2 h. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL x 3), dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 200:1). Compound 5-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (57.3 mg, 186.63 umol, 45.86% yield, 99.604% purity) was obtained as a white solid. The purity and structure of product was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 306.1 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ =12.26 (s, 1H), 8.62 - 8.51 (m, 2H), 7.76 (s, 1H), 7.20 (s, 1H), 3.83 - 3.68 (m, 1H), 1.68 (br dd, *J*=3.1, 12.7 Hz, 2H), 1.60 - 1.50 (m, 2H), 1.42 (br d, *J*=13.0 Hz, 2H), 1.34 - 1.24 (m, 2H), 0.96 (s, 3H), 0.94 (s, 3H).

Example 19a. MPL-136

Synthesis of 5,7-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide



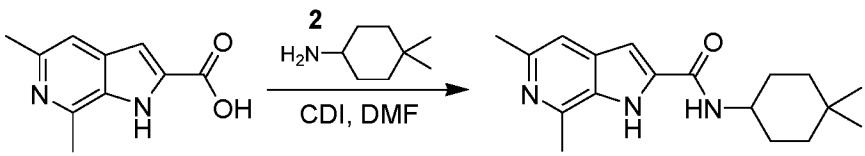
7 MPL-136

CDI (59.68 mg, 368.04 umol, 1.4 *eq*) was added to a solution of 5,7-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 262.88 umol, 1 *eq*) in DMF (2.0 mL) and stirred at 30 °C for 0.5 h. Then, (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (68.49 mg, 446.90 umol, 1.7 *eq*) was added above solution and stirred at 30 °C for 12 h. LCMS showed the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3) and the organic phase was washed with water (10 mL x 3) and brine (10 mL x 3) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1). Compound 5,7-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (13.6 mg, 41.79 umol, 15.90% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 326.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ =11.84 (br s, 1H), 8.49 (br d, *J*=8.6 Hz, 1H), 7.25 (s, 1H), 7.07 (s, 1H), 4.45 - 4.29 (m, 1H), 2.66 (s, 3H), 2.43 (s, 3H), 2.42 - 2.28 (m, 2H), 2.12 - 2.02 (m, 1H), 1.93 (br s, 1H), 1.79 (br t, *J*=5.1 Hz, 1H), 1.74 - 1.65 (m, 1H), 1.22 - 1.18 (m, 4H), 1.07 - 1.02 (m, 6H).

Example 20. MPL-137

Synthesis of N-(4,4-dimethylcyclohexyl)-5,7-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



1 MPL-137

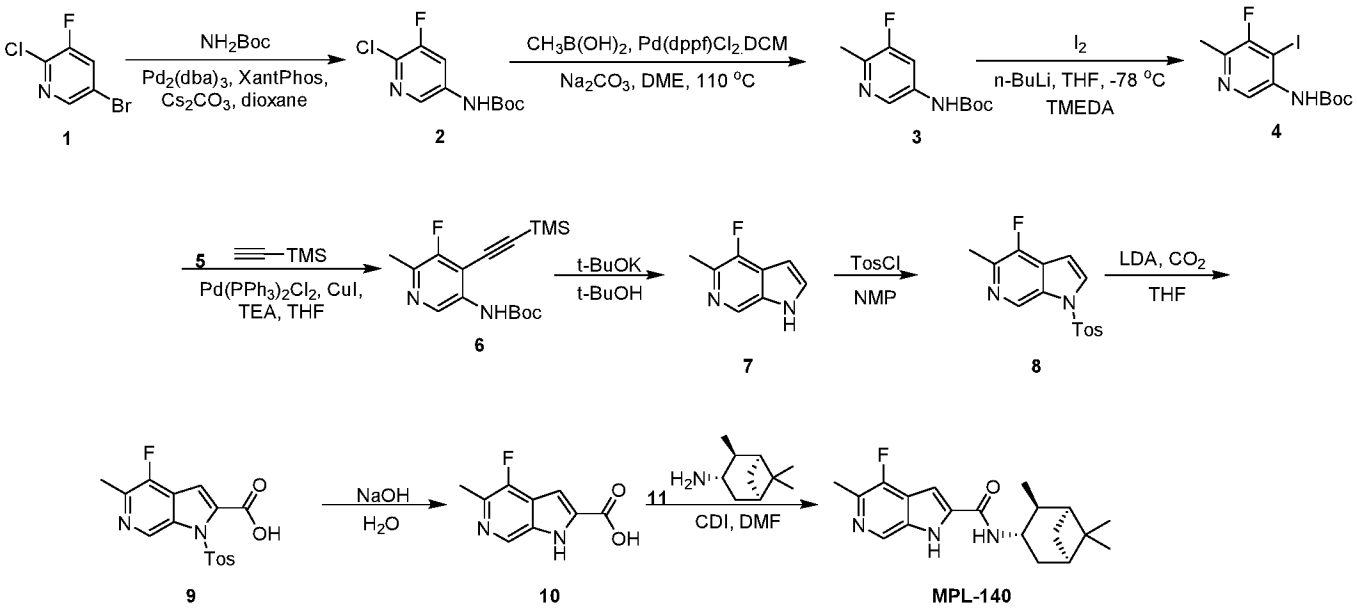
CDI (55.41 mg, 341.75 umol, 1.3 *eq*) was added to a solution of 5,7-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 262.88 umol, 1 *eq*) in DMF (2.0 mL) and stirred at 30 °C

for 0.5 h. Then, 4,4-dimethylcyclohexanamine (50.17 mg, 394.33 umol, 1.5 *eq*) was added above solution and stirred at 30 °C for 12 h. LCMS showed the starting material was consumed completely and the desired MS was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3) and the organic phase was washed with water (10 mL x 3) and brine (10 mL x 3) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 25%-50%,11min). The obtained compound was not pure. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 13:1). CompoundN-(4,4-dimethylcyclohexyl)-5,7-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (6.4 mg, 21.38 umol, 8.13% yield, 100% purity) was obtained as a white solid.

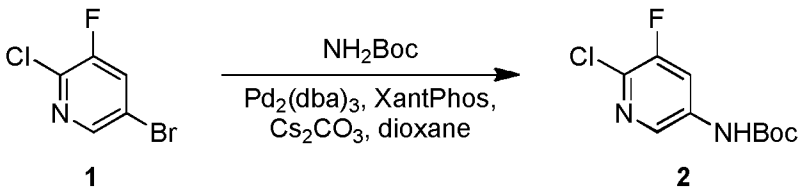
LCMS (ESI) m/z: 300.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ =11.87 (br s, 1H), 8.39 (br d, *J*=8.1 Hz, 1H), 7.26 (s, 1H), 7.06 (s, 1H), 3.83 - 3.66 (m, 1H), 2.69 (s, 3H), 2.45 (s, 3H), 1.72 - 1.63 (m, 2H), 1.61 - 1.47 (m, 2H), 1.45 - 1.37 (m, 2H), 1.30 (br dd, *J*=3.5, 13.2 Hz, 2H), 0.94 (d, *J*=8.7 Hz, 6H).

Example 21. MPL-140

Scheme



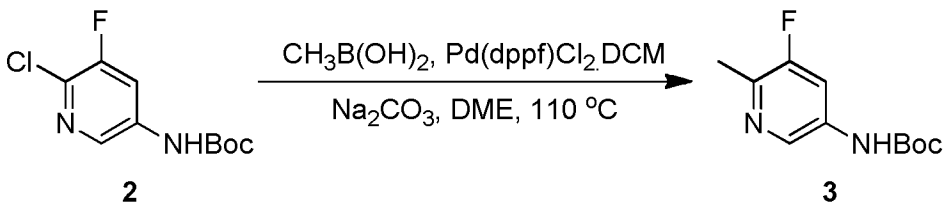
Synthesis of tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate



1 2

To a solution of 5-bromo-2-chloro-3-fluoro-pyridine (16 g, 76.03 mmol, 1 *eq*) and tert-butyl carbamate (9.35 g, 79.84 mmol, 1.05 *eq*) in dioxane (200 mL) was added $Pd_2(dba)_3$ (2.09 g, 2.28 mmol, 0.03 *eq*) Xantphos (4.40 g, 7.60 mmol, 0.1 *eq*) and Cs_2CO_3 (49.55 g, 152.07 mmol, 2 *eq*). The mixture was stirred at 85 °C for 24 hr under N_2. TLC and LC-MS showed the starting material was consumed completely and one main peak with desired MS was detected. The mixture was diluted with EtOAc (100ml) and washed with H_2O (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1;0 to 5:1). The product tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (16.7 g, 47.39 mmol, 62.33% yield, 70% purity) was obtained as yellow solid. LCMS (ESI) m/z 247.0 $[M+H]^+$

Synthesis of tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate

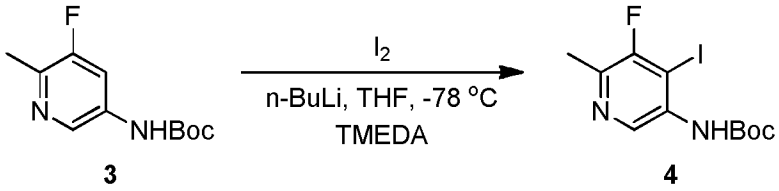


2 3

To a solution of methylboronic acid (18.20 g, 304.06 mmol, 5 *eq*) in DME (200 mL) and H_2O (20 mL) was added tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (15 g, 60.81 mmol, 1 *eq*) $Pd(dppf)Cl_2.CH_2Cl_2$ (2.48 g, 3.04 mmol, 0.05 *eq*) and Na_2CO_3 (19.34 g, 182.43 mmol, 3 *eq*). The mixture was stirred at 120 °C for 36 hr. TLC and LCMS showed the desired MS was detected. The mixture was filtered and the filter was washed with brine (100 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO2, Petroleum ether/EtOAc=1:0 to 5:1). The product tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate (9.6 g, 38.19 mmol, 62.80% yield, 90% purity) was obtained as brown oil and purity comes from H NMR.

LCMS (ESI) m/z 227.2 $[M+H]^+$

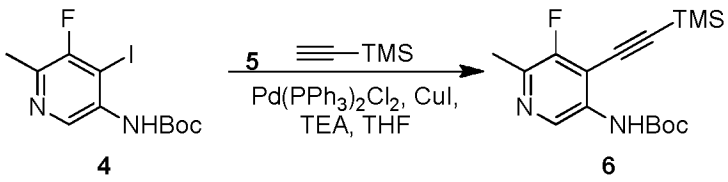
Synthesis of tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl)carbamate



To a solution of tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate (3 g, 13.26 mmol, 1 *eq*) and TMEDA (4.62 g, 39.78 mmol, 6.00 mL, 3 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 26.52 mL, 5 *eq*) at -78 °C under N_2. The mixture was stirred for 0.5 h at the same temperature and the I_2 (10.10 g, 39.78 mmol, 8.01 mL, 3 *eq*) (in 20 ml THF) was dropwise added, the mixture was stirred for 11.5 h at the -78 °C under N_2. TLC and LC-MS showed the desired MS was detected. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (50 mL) and saturated aqueous Na_2SO_3 (100 mL), and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 20:1). The product tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl)carbamate (3.6 g, 9.20 mmol, 69.39% yield, 90% purity) was obtained as white solid.

LCMS (ESI) m/z 352.9 $[M+H]^+$

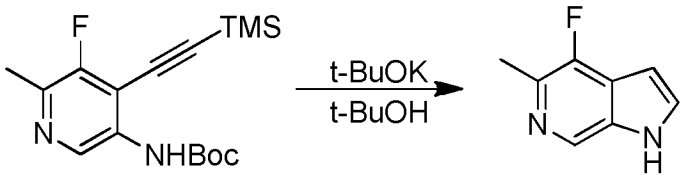
Synthesis of tert-butyl N-[5-fluoro-6-methyl-4-(2-trimethylsilylethynyl)-3-pyridyl] carbamate



To a solution of tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl)carbamate (3.4 g, 9.66 mmol, 1 *eq*) in THF (30 mL) was added TEA (2.93 g, 28.97 mmol, 4.03 mL, 3 *eq*), CuI (367.77 mg, 1.93 mmol, 0.2 *eq*) and $Pd(PPh3)_2Cl_2$ (677.69 mg, 965.52 umol, 0.1 *eq*) under N_2. Then

ethynyl(trimethyl)silane (2.84 g, 28.97 mmol, 4.01 mL, 3 *eq*) was added to the mixture, the mixture was stirred at 20 °C for 12 hr under N_2. TLC (Petroleum ether : EtOAc = 5 : 1, Rf = 0.5) indicated reactant was consumed completely and many new spots formed. The solvent was removed under reduced pressure to afford the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% EtOAc/Petroleum ether gradient at 40 mL/min). Compound tert-butyl N-[5-fluoro-6-methyl-4-(2-trimethylsilylethynyl)-3-pyridyl]carbamate (3.1 g, 6.73 mmol, 69.70% yield, 70% purity) was obtained as a brown solid.

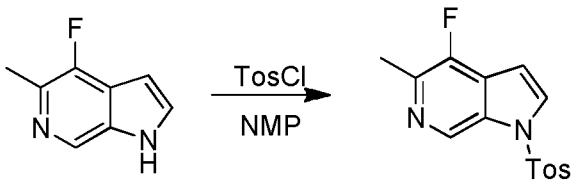
Synthesis of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine



6 **7**

To a solution of tert-butyl N-[5-fluoro-6-methyl-4-(2-trimethylsilylethynyl)-3-pyridyl]carbamate (2.4 g, 7.44 mmol, 1 *eq*) in t-BuOH (50 mL) was added t-BuOK (2.51 g, 22.33 mmol, 3 *eq*). The mixture was stirred at 80 °C for 12 hr. TLC (Petroleum ether : EtOAc = 2 : 1, Rf = 0.2) indicated reactant was consumed completely, and one major new spot with larger polarity was detected. The mixture was used directly to the next step without work-up. Compound 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine (1.12 g, crude) was in solution of t-BuOH.

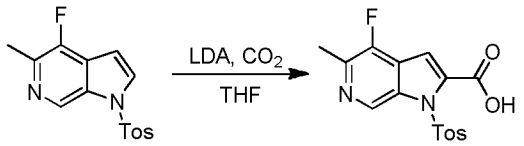
Synthesis of 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine



7 **8**

To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine (1.12 g, 7.46 mmol, 1 *eq*) in t-BuOH (50 mL) was added t-BuOK (2.51 g, 22.38 mmol, 3 *eq*) and 4-methylbenzenesulfonyl chloride (2.13 g, 11.19 mmol, 1.5 *eq*). The mixture was stirred at 20 °C for 12 hr. TLC indicated reactant was consumed completely and two new spots formed. LCMS showed one major peak with desired mass. The solvent was removed under reduced pressure, product was redissolved in EtOAc (20 mL), and organic layer was washed with water (20 mL) and Sat. NaCl (in water, 20 mL). The separated organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product which was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% EtOAc/Petroleum ether gradient at 36 mL/min). Compound 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (1.98 g, 6.38 mmol, 85.48% yield, 98% purity) was obtained as a white solid. LCMS (ESI) m/z 305.1 $[M+H]^+$

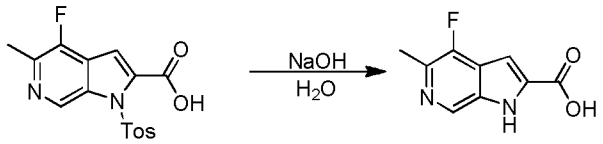
Synthesis of 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid



8 **9**

To a solution of 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (1.7 g, 5.59 mmol, 1 *eq*) in THF (20 mL) (dried by Na and distilled) was added LDA (2 M, 4.19 mL, 1.5 *eq*) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 1.5 hr. Then N_2 balloon was exchanged with CO_2 balloon quickly, the mixture was allowed warm to 20 °C gradually and stirred under CO_2 for 12 hr. LC-MS showed reactant was consumed completely and two peaks which one of them with desired mass were detected. The reaction mixture was filtered under reduce pressure; filter cake was washed with EtOAc (10mL x 3). The product was used directly to the next step without further purification. Compound 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2- carboxylic acid (2.1 g, crude) was obtained as a yellow solid. LCMS (ESI) m/z 349.0 $[M+H]^+$

Synthesis of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

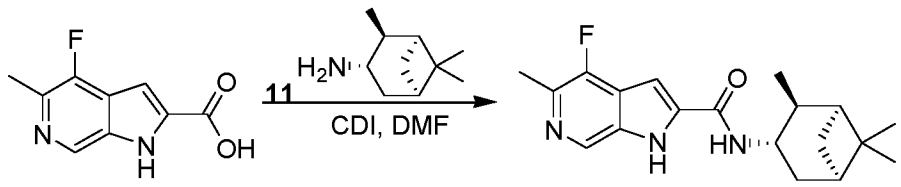


9 10

The 4-fluoro-5-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid (2.1 g, 6.03 mmol, 1 *eq*) was redissovled in NaOH (2 M, 20 mL, 6.63 *eq*). The mixture was stirred at 20 °C for 12 hr.

LC-MS showed reactant was consumed completely and one main peak with desired mass was detected. HCl (6 M, in water) was added into the reaction mixture to adjust pH = 5. Filtered, the filter cake was washed with water (20 mL x 2). Compound 4-fluoro-5-methyl-1H-pyrrolo [2,3-c]pyridine-2-carboxylic acid (545 mg, 2.75 mmol, 45.62% yield, 98% purity) was obtained as a white solid. LCMS (ESI) m/z 195.0 $[M+H]^+$

Synthesis of 4-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H -pyrrolo[2,3-c]pyridine-2-carboxamide



10 MPL-140

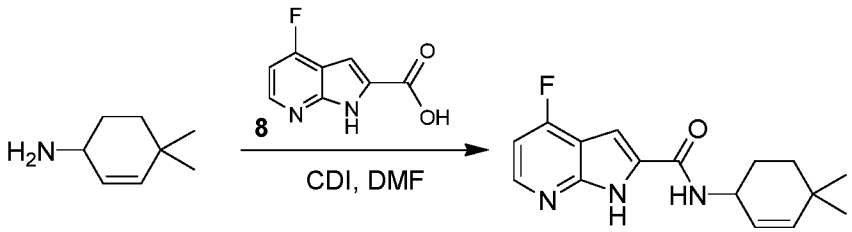
To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (0.1 g, 515.03 umol, 1 *eq*) in DMF (3 mL) (dried by CaH_2) was added CDI (100.21 mg, 618.04 umol, 1.2 *eq*), the mixture was stirred at 20 °C for 0.5 hr. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (94.72 mg, 618.04 umol, 1.2 *eq*) was added, the mixture was stirred at 20 °C for 1 hr. LC-MS showed reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was dropped into water (20 mL). The product was isolated as white solid. Filtered, the filter cake was washed with water (5mL xv2) to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% EtOAc/Petroleum ether gradient at 40 mL/min).All fractions

found to contain product by TLC (Petroleum ether: EtOAc = 3:1, Rf = 0.4) were combined and evaporated. Compound 4-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (15 mg, 45.54 umol, 8.84% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 330.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ =12.16 (br s, 1 H) 8.50 (d, *J*=8.54 Hz, 1 H) 8.43 (d, *J*=2.14 Hz, 1 H) 7.21 (s, 1 H) 4.25 - 4.34 (m, 1 H) 2.38 (d, *J*=3.20 Hz, 3 H) 2.32 - 2.36 (m, 1 H) 2.25 - 2.31 (m, 1 H) 1.94 - 2.04 (m, 1 H) 1.81 - 1.89 (m, 1 H) 1.72 (t, *J*=5.26 Hz, 1 H) 1.62 (ddd, *J*=13.69, 6.45, 2.14 Hz, 1 H) 1.14 (s, 3 H) 1.11 (d, *J*=9.61 Hz, 1 H) 0.95 - 1.00 (m, 6 H).

Example 22. MPL-160

Synthesis of N-(4,4-dimethylcyclohex-2-en-1-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



7 MPL-160

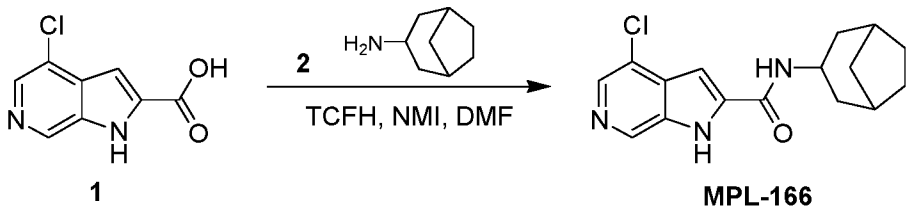
To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added 4,4-dimethylcyclohex-2-en-1-amine (116.67 mg, 721.68 umol, 1.3 *eq*, HCl), 1-methylimidazole (182.31 mg, 2.22 mmol, 177.00 uL, 4 *eq*) and [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (202.49 mg, 721.68 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were trace starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 45%-70%,11min). Compound N-(4,4-dimethylcyclohex-2-en-1-yl)- 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (20 mg, 69.61

umol, 12.54% yield, 100% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 288.1 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d6) δ =12.44 (br s, 1H), 8.45 (br d, *J*=7.8 Hz, 1H), 8.30 (dd, *J*=5.4, 8.3 Hz, 1H), 7.28 (s, 1H), 6.99 (dd, *J*=5.4, 10.3 Hz, 1H), 5.58 - 5.52 (m, 1H), 5.48 - 5.42 (m, 1H), 4.49 - 4.40 (m, 1H), 1.84 (br d, *J*=5.4 Hz, 1H), 1.70 - 1.54 (m, 2H), 1.49 - 1.40 (m, 1H), 1.02 (s, 3H), 0.97 (s, 3H).

Example 23. MPL-166

Synthesis of N-(3-bicyclo[3.2.1]octanyl)-4-chloro-1H-pyrrolo[2,3-c]pyridine-2- carboxamide

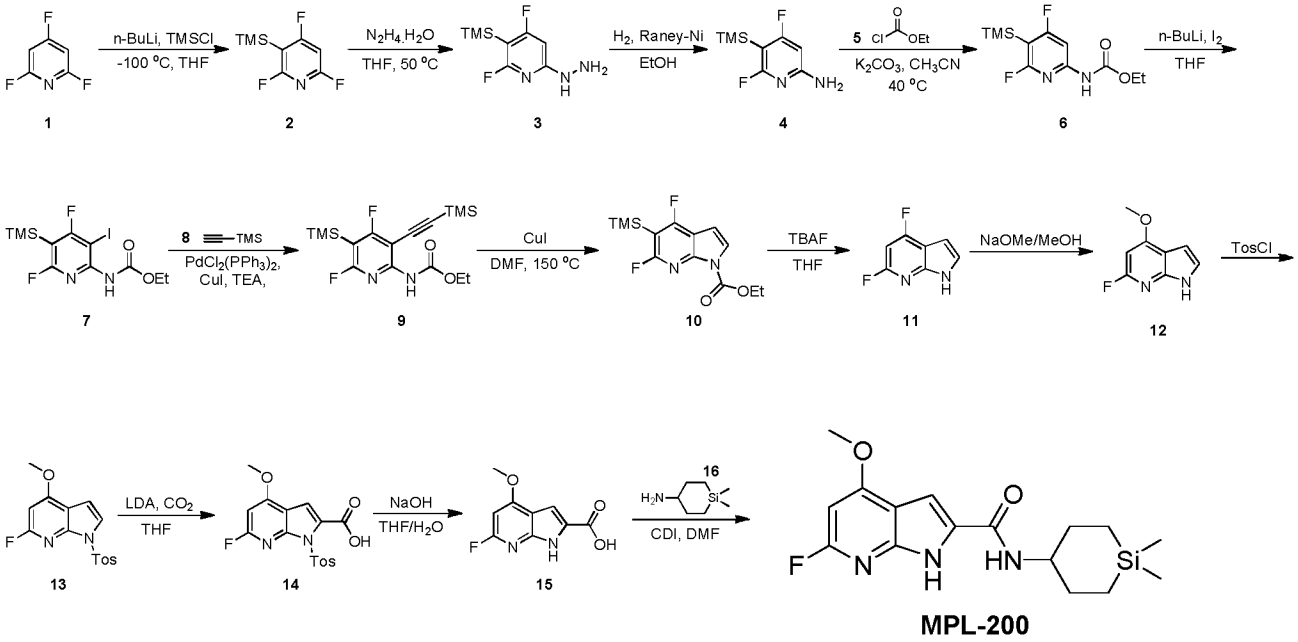


To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) in DMF (1 mL) was added bicyclo[3.2.1]octan-3-amine (49.34 mg, 305.20 umol, 1.2 *eq*, HCl), 1-methylimidazole (83.53 mg, 1.02 mmol, 81.09 uL, 4 *eq*) and [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (92.77 mg, 330.64 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN]; B%: 30%-58%,11min). Compound N-(3-bicyclo[3.2.1]octanyl)-4-chloro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (20 mg, 65.84 umol, 25.89% yield, 100% purity) was obtained as a white solid.

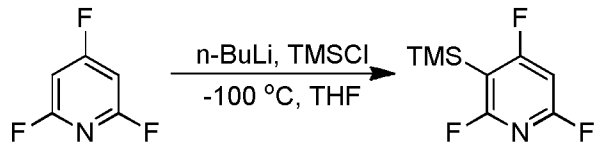
LCMS (ESI) m/z 304.1 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ =12.48 (br s, 1H), 8.73 (s, 1H), 8.53 (br d, *J*=6.8 Hz, 1H), 8.19 (s, 1H), 7.32 (s, 1H), 4.20 - 4.07 (m, 1H), 2.24 (br s, 2H), 1.73 (br d, *J*=12.2 Hz, 2H), 1.69 - 1.58 (m, 2H), 1.52 (br d, *J*=7.6 Hz, 2H), 1.46 - 1.32 (m, 4H).

Example 24. MPL-200

Scheme

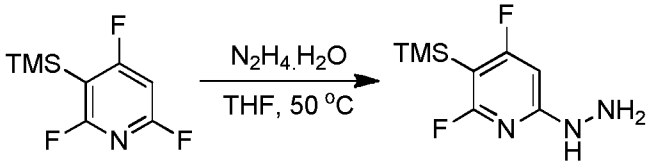


Synthesis of trimethyl-(2,4,6-trifluoro-3-pyridyl)silane



At -100 °C 2,4,6-trifluoropyridine (5 g, 37.57 mmol, 1 *eq*) in THF (78 mL) was added dropwise n-BuLi (2.5 M, 15.78 mL, 1.05 *eq*) in hexane. After 45 min at -100 °C, chloro(trimethyl)silane (4.08 g, 37.57 mmol, 4.77 mL, 1 *eq*) was added in one portion, after 45 min at -75 °C. TLC showed the starting material was consumed. The reaction solution was quenched by aq. sat. NH_4Cl (40 mL), extracted with petroleum ether (50 mL x 2). The organic layers were dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a liquid. The liquid was purified by column chromatography (SiO_2, petroleum ether). Compound trimethyl-(2,4,6-trifluoro-3-pyridyl)silane (6.0 g, 27.77 mmol, 73.91% yield, 95% purity) was obtained as a colorless liquid.

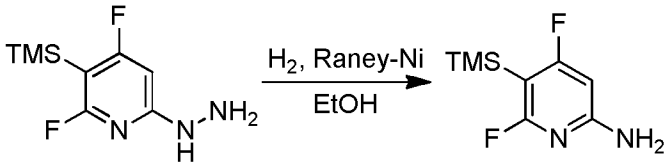
Synthesis of (4,6-difluoro-5-trimethylsilyl-2-pyridyl)hydrazine



2 **3**

To a solution of trimethyl-(2,4,6-trifluoro-3-pyridyl)silane (9 g, 43.85 mmol, 1 *eq*) in THF (80 mL) was added $NH_2NH_2.H_2O$ (5.16 g, 87.70 mmol, 5.01 mL, 2 *eq*). The mixture was stirred at 50 °C for 2 hr. TLC showed the desired product was detected. The mixture was concentrated in reduced pressure. The residue was diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The crude product was purified by silica column chromatography (SiO_2, petroleum ether/EtOAc = 50/1 to 5/1). Compound (4,6-difluoro-5-trimethylsilyl-2-pyridyl)hydrazine (4.5 g, 18.64 mmol, 42.51% yield, 90% purity) was obtained as a yellow solid.

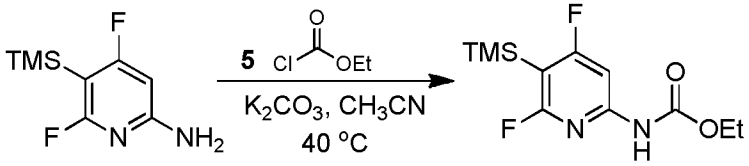
Synthesis of 4,6-difluoro-5-trimethylsilyl-pyridin-2-amine



3 **4**

To a solution of (4,6-difluoro-5-trimethylsilyl-2-pyridyl)hydrazine (5 g, 23.01 mmol, 1 *eq*) in EtOH (65 mL) was added Raney-Ni (394.29 mg, 2.30 mmol, 50% purity, 0.1 *eq*) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (20 psi) at 30 °C for 48 hours. TLC showed the starting material was consumed. The mixture was filtered and the filter cake was washed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure to give 4,6-difluoro-5-trimethylsilyl-pyridin-2-amine (4.58 g, 18.11 mmol, 78.72% yield, 80% purity) as a yellow solid.

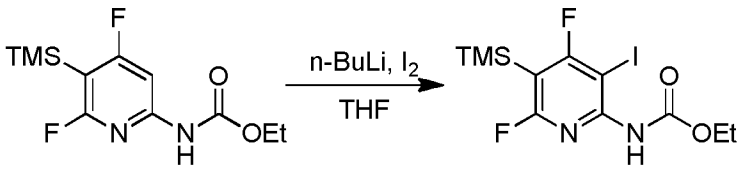
Synthesis of ethyl N-(4,6-difluoro-5-trimethylsilyl-2-pyridyl)carbamate



4 **6**

To a solution of 4,6-difluoro-5-trimethylsilyl-pyridin-2-amine (4.58 g, 22.64 mmol, 1 *eq*) and Py (7.16 g, 90.57 mmol, 7.31 mL, 4 *eq*) in DCM (45 mL) was added ethyl carbonochloridate (9.83 g, 90.57 mmol, 8.62 mL, 4 *eq*) dropwise at 0 °C under N_2. The mixture was stirred at 20 °C for 15 min. TLC showed the starting material was consumed, and one new spot was formed. The mixture was quenched with sat. $NaHCO_3$ (20 mL), extracted with EtOAc (20 mL X 2). The organic layers were washed with 0.5 M aq. HCl (20 mL x 2) and dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a liquid. The liquid was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 100/1 to 10/1). Compound ethyl N-(4,6-difluoro-5-trimethylsilyl-2-pyridyl)carbamate (5.4 g, 17.72 mmol, 78.24% yield, 90% purity) was obtained as a yellow liquid.

Synthesis of ethyl N-(4,6-difluoro-3-iodo-5-trimethylsilyl-2- pyridyl)carbamate

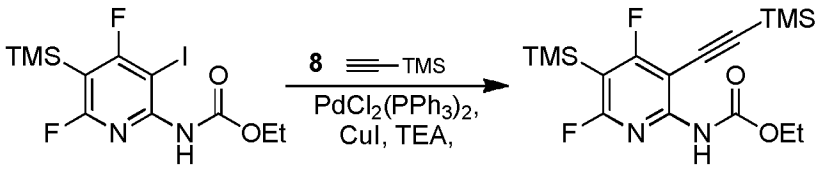


6 **7**

To a solution of ethyl N-(4,6-difluoro-5-trimethylsilyl-2-pyridyl)carbamate (4.4 g, 16.04 mmol, 1 *eq*) and TMEDA (3.73 g, 32.08 mmol, 4.84 mL, 2 *eq*) in THF (30 mL) was added n-BuLi (2.5 M, 12.83 mL, 2 *eq*) dropwise at -78 °C for 0.5 hr under N_2. Then I_2 (8.14 g, 32.08 mmol, 6.46 mL, 2 *eq*) in THF (14 mL) was added into above solution at -78 °C for 1 hr. TLC showed the starting material was consumed. The reaction was quenched by sat. NH_4Cl (50 mL), extracted with EtOAc (50 mL x 3). The organic layers were dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column

chromatography (SiO_2, petroleum ether/ EtOAc = 100/1 to 10/1). Compound ethyl N-(4,6-difluoro-3-iodo-5-trimethylsilyl-2- pyridyl)carbamate (4.5 g, 10.12 mmol, 63.09% yield, 90% purity) was obtained as a yellow liquid.

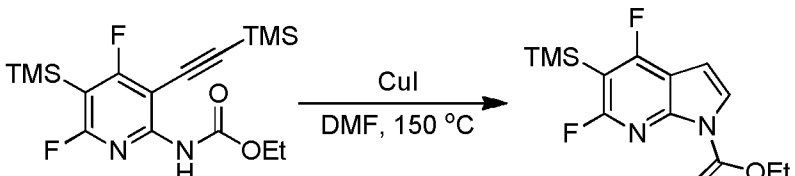
Synthesis of N-[4,6-difluoro-5-trimethylsilyl-3- (2-trimethylsilylethynyl)-2-pyridyl]carbamate



7 9

ethyl N-(4,6-difluoro-3-iodo-5-trimethylsilyl-2-pyridyl)carbamate (4.5 g, 11.24 mmol, 1 *eq*), ethynyl-trimethyl-silane (11.04 g, 112.43 mmol, 15.58 mL, 10 *eq*) and $Pd(PPh3)_2Cl_2$ (789.17 mg, 1.12 mmol, 0.1 *eq*), CuI (642.39 mg, 3.37 mmol, 0.3 *eq*) in TEA (45 mL) was de-gassed and then heated to 80 °C for 12 hours under N_2. LCMS showed the desired product was detected. The mixture was diluted with EtOAc (50 mL) and washed with water (50 mL) and aq. 1 M HCl (50 mL x 2). The organic layer was dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 100/1 to 10/1). Compound ethyl N-[4,6-difluoro-5-trimethylsilyl-3-(2-trimethylsilylethynyl)-2-pyridyl]carbamate (4 g, 9.18 mmol, 81.61% yield, 85% purity) was obtained as a yellow solid. LCMS (ESI), m/z 371.4 $[M+H]^+$

Synthesis of ethyl 4,6-difluoro-5-trimethylsilyl-pyrrolo[2,3-b]pyridine-1-carboxylate

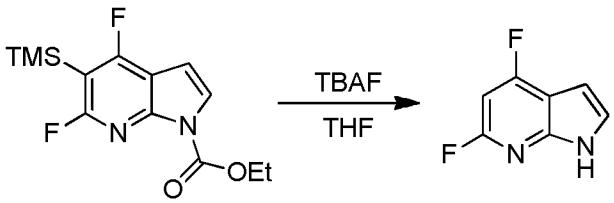


9 10

The mixture of ethyl N-[4,6-difluoro-5-trimethylsilyl-3-(2-trimethylsilylethynyl)-2-pyridyl] carbamate (4 g, 9.18 mmol, 1 *eq*) and CuI (3.50 g, 18.35 mmol, 2 *eq*) in DMF (40 mL) was stirred at 150 °C for 2 hr. LCMS showed the desired product was detected. The mixture was

diluted with EtOAc (200 mL) and washed with 3% aq. LiCl (40 mL x 2), following by brine (40 mL). The organic phase was dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 100/1 to 10/1). Compound ethyl 4,6-difluoro-5-trimethylsilyl-pyrrolo[2,3-b]pyridine-1-carboxylate (1.1 g, 3.50 mmol, 38.14% yield, 95% purity) was obtained as a yellow solid. LCMS (ESI), m/z 371.4 $[M+H]^+$

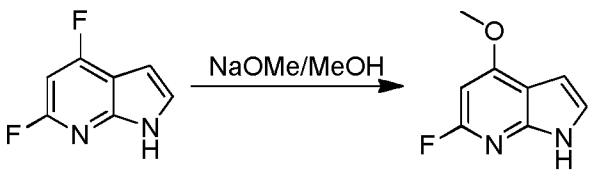
Synthesis of 4,6-difluoro-1H-pyrrolo[2,3-b]pyridine



10 **11**

Ethyl 4,6-difluoro-5-trimethylsilyl-pyrrolo[2,3-b]pyridine-1-carboxylate (1.1 g, 3.69 mmol, 1 *eq*) was dissolved to TBAF (1 M, 11.00 mL, 2.98 *eq*) (In THF) was stirred at 25 °C for 12 hr. TLC showed the starting material was consumed. The mixture was quenched by water (20 mL) and extracted with EtOAc (30 mL x 2). The organic layers were washed with brine (30 mL) dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 100/1 to 10/1). Compound 4,6-difluoro-1H-pyrrolo[2,3-b]pyridine (560 mg, crude) was obtained as a yellow solid.

Synthesis of 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine

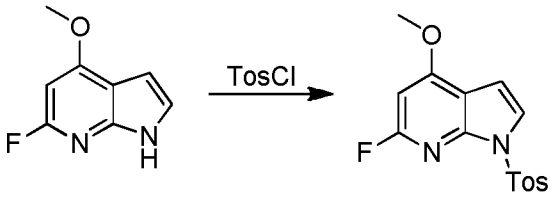


11 **12**

A mixture of 4,6-difluoro-1H-pyrrolo[2,3-b]pyridine (560 mg, 3.63 mmol, 1 *eq*) and NaOMe (392.60 mg, 7.27 mmol, 2 *eq*) in MeOH (5.6 mL) was stirred at 50 °C for 12 hr. LCMS showed

the starting material was consumed and the desired product was detected. The mixture was diluted with EtOAc (10 mL) and washed with water (5 mL), follow by brine (5 mL). The organic layer was dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, petroleum ether/EtOAc = 3/1). Compound 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine (400 mg, 2.41 mmol, 66.25% yield, 100% purity) was obtained as a white solid. LCMS (ESI), m/z 166.9$[M+H]^+$

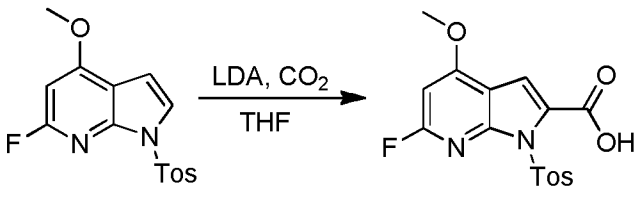
Synthesis of 6-fluoro-4-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine



12 **13**

To a solution of 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine (444 mg, 2.67 mmol, 1 *eq*),TEA (811.22 mg, 8.02 mmol, 1.12 mL, 3 *eq*) and DMAP (65.29 mg, 534.45 umol, 0.2 *eq*) in THF (10 mL) was added TosCl (1.02 g, 5.34 mmol, 2 *eq*). The mixture was stirred at 30 °C for 12 hr. LCMS showed 75 % desired product was detected and 25 % starting material was remained. The mixture was diluted with EtOAc (40 mL) and washed with water (20 mL x 2), follow by brine (20 mL). The organic layer was dried over Na_2SO_4 and filtered and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography (SiO_2, petroleum ether/EtOAc = 50/1 to 5/1). Compound 6-fluoro-4-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine (686 mg, 1.61 mmol, 60.10% yield, 75% purity) as a yellow solid. LCMS (ESI), m/z 321.1 $[M+H]^+$

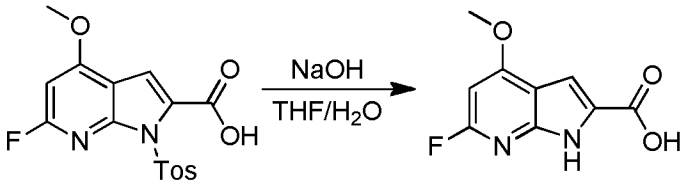
Synthesis of 6-fluoro-4-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid



13 **14**

To a solution of 6-fluoro-4-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (450 mg, 1.40 mmol, 1 *eq*) in THF (6 mL) was added dropwise LDA (2 M, 1.40 mL, 2 *eq*) at -78 °C under N_2. The mixture was stirred at -78 °C for 1 hr under N2. Then the mixture was stirred at -78 °C for 0.5 hr under CO_2 (15 psi) atmosphere. LCMS showed there was no starting material and main desired compound was detected. The reaction was not worked up and the reaction solution was used into next step. LCMS (ESI), m/z 365.0 $[M+H]^+$

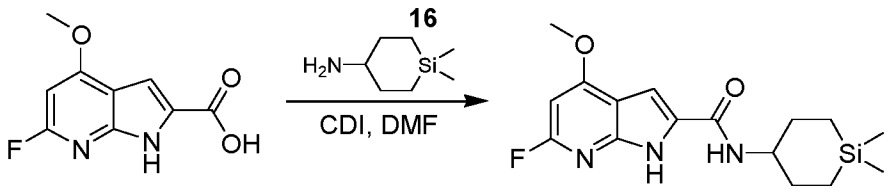
Synthesis of 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



14 **15**

Aqueous solution NaOH (2 M, 6 mL, 8.56 *eq*) was added into 6-fluoro-4-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (511 mg, 1.40 mmol, 1 *eq*) in above step solution (6 m THF) under N_2 and stirred at 70 °C for 1 hr. LCMS showed the desired product was detected. The reaction solution was concentrated under reduced pressure to remove THF, and the aqueous solution was extracted with EtOAc (5 mL x 2). The aqueous solution was neutralized with aq. 2 M HCl to pH = 4. Then the precipitate was formed, filtered and the filter cake was collected. Compound 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (120 mg, 342.59 umol, 24.43% yield, 60% purity) was obtained as a white solid. LCMS (ESI), m/z 211.0 $[M+H]^+$

Synthesis of N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



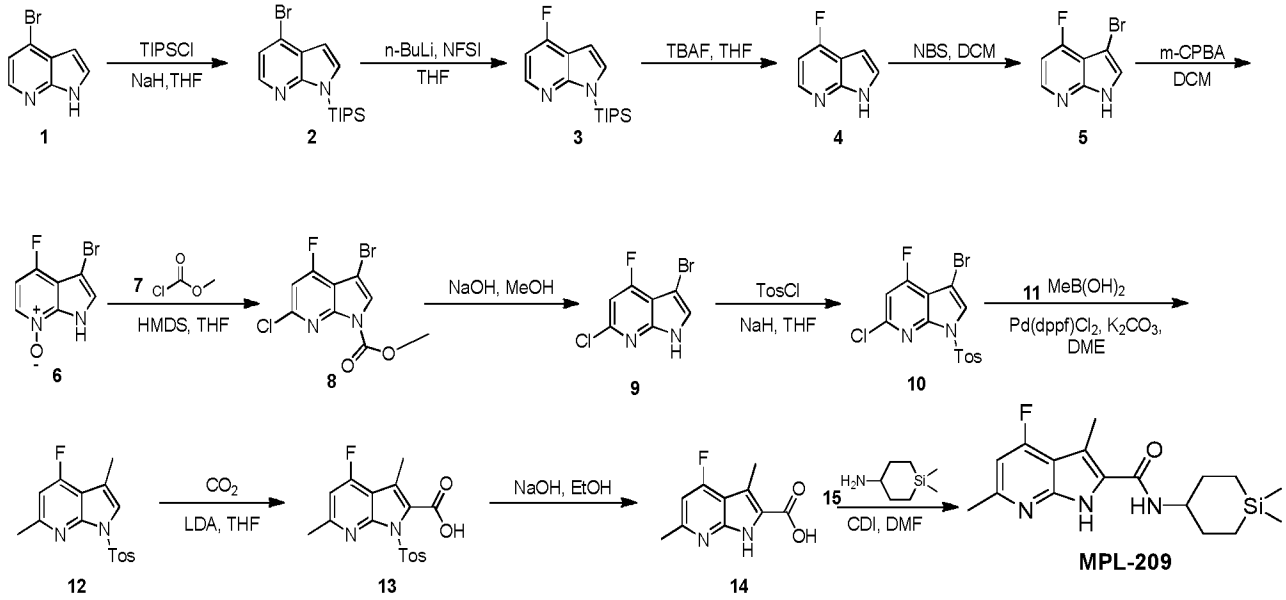
15 **MPL-200**

To a solution of 6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (120 mg, 570.99 umol, 1 *eq*) in DMF (2 mL) was added CDI (97.21 mg, 599.54 umol, 1.05 *eq*) under N_2, the mixture was stirred at 30 °C for 1 hr. 1,1-dimethylsilinan-4-amine (97.80 mg, 682.49 umol, 1.2 *eq*) was added to above solution and stirred at 30 °C for 1 hr. LCMS showed the desired product was detected. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 55%-85%,10min). CompoundN-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (44 mg, 130.98 umol, 23.03% yield, 99.86% purity) was obtained as a white solid.

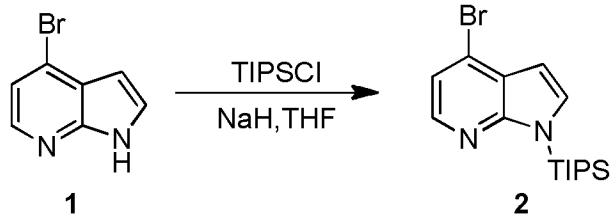
LCMS (ESI), m/z 336.1 $[M+H]^+$;1H NMR (500MHz, DMSO-d6) δ = 12.06 (s, 1H), 8.04 (d, *J*=8.1 Hz, 1H), 7.10 (s, 1H), 6.38 (s, 1H), 3.97 - 3.81 (m, 3H), 3.70 - 3.48 (m, 1H), 1.89 (br d, *J*=9.3 Hz, 2H), 1.67 - 1.37 (m, 2H), 0.69 (br d, *J*=14.5 Hz, 2H), 0.51 (dt, *J*=4.7, 14.1 Hz, 2H), 0.02 - -0.09 (m, 6H).

Example 25. MPL-209

Scheme



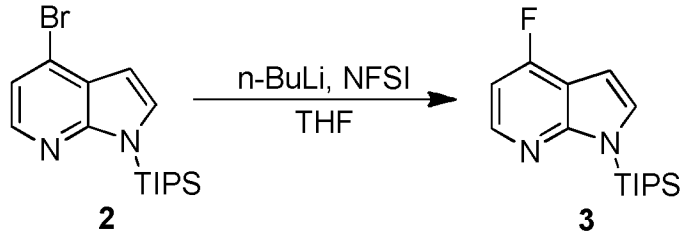
(4-bromopyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



1 2

To a solution of NaH (2.54 g, 63.44 mmol, 60% purity, 2.5 *eq*) in THF (50 mL) was added 4-bromo-1H-pyrrolo[2,3-b]pyridine (5 g, 25.38 mmol, 1 *eq*) and chlorotriisopropylsilane (7.34 g, 38.06 mmol, 8.15 mL, 1.5 *eq*). The mixture was stirred at 0 °C. The mixture was stirred at 10 °C for 12 h. LCMS showed no starting material. TLC (Petroleum ether:EtOAc =5:1,Rf=1) showed one new spots was observed. The reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl. The mixture was concentrated in reduced pressure. The resulting solution was extracted with EtOAc (15mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 1:0 to 3:1). The product (4-bromopyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (8.9 g, 22.67 mmol, 89.32% yield, 90% purity) was obtained as white solid. LCMS (ESI) m/z 355.0 $[M+H]^+$

(4-fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane

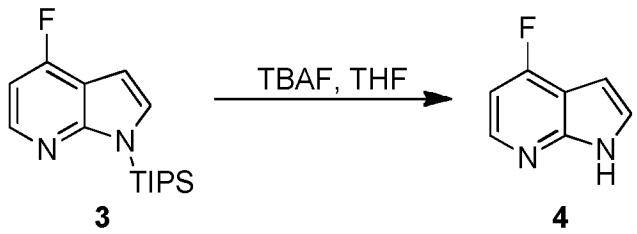


2 3

To a solution of (4-bromopyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (15 g, 42.45 mmol, 1 *eq*) in THF(150 mL) was added n-BuLi (2.5 M, 33.96 mL, 2 *eq*) at -78°C under N_2. The mixture was stirred at -78 °C for 0.5 h under N_2. A solution of NFSI (20 g, 63.42 mmol, 1.49 *eq*) in THF (50 mL) was added at -78 °C. The mixture was stirred at 10 °C for 11.5 h under N_2. LCMS showed no starting material. TLC (Petroleum ether/EtOAc=1:0, Rf= 1)showed new spots was observed. The reaction was quenched with saturated aqueous NH_4Cl (30mL). The mixture was concentrated in reduced pressure. The residue was diluted with H_2O (20 mL). The aqueous

phase was extracted with EtOAc (50 mL x 3) and washed with water (50ml x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0). The product (4-fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9.3 g, 28.62 mmol, 67.42% yield, 90% purity) was obtained as yellow brown oil. LCMS (ESI) m/z 293.2 $[M+H]^+$

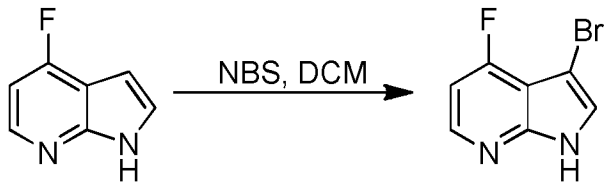
4-fluoro-1H-pyrrolo[2,3-b]pyridine



3 **4**

To a solution of (4-fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (17 g, 58.13 mmol, 1 *eq*) in THF (50 mL) was added TBAF(solution in THF) (1 M, 85.00 mL, 1.46 *eq*). The mixture was stirred at 10 °C for 2 h. LCMS showed no starting material. TLC (Petroleum ether/EtOAc=5:1,Rf=0.15) showed no starting material and new spots was observed. The mixture was concentrated in reduced pressure. The residue was diluted with EtOAc (30 mL). The aqueous phase was washed with H_2O (30 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, **Petroleum ether/EtOAc=1:0 to 3:1**). The product 4-fluoro-1H-pyrrolo[2,3-b]pyridine (10 g, 55.10 mmol, 94.79% yield, 75% purity) was obtained as white solid. LCMS (ESI) m/z 137.0 $[M+H]^+$

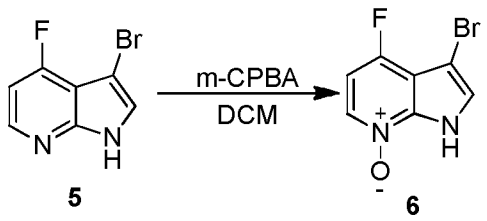
3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine



4 **5**

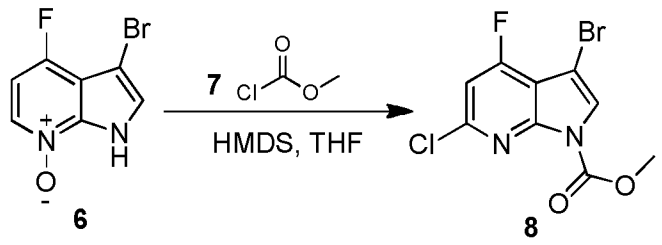
To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine (5 g, 36.73 mmol, 1 *eq*) in DCM(50 mL) was added a solution of NBS (8.50 g, 47.75 mmol, 1.3 *eq*) in DCM (50 mL) at 0° C. The mixture was stirred at 10 °C for 12 h. LCMS showed desired massdesired mass was detected. TLC (Petroleum ether/EtOAc=3:1, Rf=0.10) showed new spots was observed. The mixture was filtered and the filter cake was washed with 30 mL x 3 of DCM. The aqueous phase was washed with 30 mL x 3 of water. The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 3:1). The product 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine (9.7 g, 40.60 mmol, 55.27% yield, 90% purity) was obtained as yellow solid. LCMS (ESI) m/z 217.0 $[M+H]^+$

3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine 7-oxide



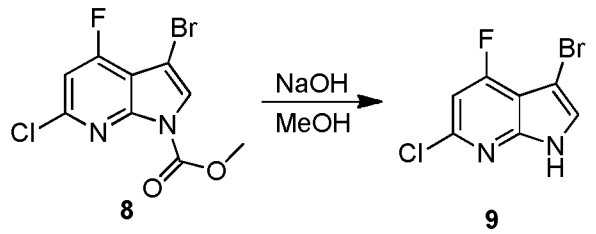
To a solution of 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine (5 g, 23.25 mmol, 1 *eq*) in DCM (50 mL) was added a solution of m-CPBA (19 g, 93.59 mmol, 85% purity, 4.02 *eq*) in DCM (100mL) at 0 °C. The mixture was stirred at 10 °C for 12 h. LCMS showed no starting material desired mass was detected. The reaction was quenched with saturated aqueous Na_2SO_3 (30mL). The mixture was filtered and the filter cake was wash with Na_2CO_3 (50mL). The mixture was filtered and the filter was product 1. The crude product was used directly for the next step without purification. The product 1 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine 7-oxide (8 g, 17.31 mmol, 37.23% yield, 50% purity) was obtained as yellow solid. LCMS (ESI) m/z $[M+H]^+$

methyl 3-bromo-6-chloro-4-fluoro-pyrrolo[2,3-b]pyridine-1-carboxylate



To a solution of 3-bromo-4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (7 g, 30.30 mmol, 1 *eq*) and HMDS (4.89 g, 30.30 mmol, 6.35 mL, 1 *eq*) in THF (100 mL) was added methyl carbonochloridate (8.59 g, 90.90 mmol, 7.04 mL, 3 *eq*) at 0 °C. Then the mixture was stirred at 10 °C for 12 h. LCMS showed the starting material was consumed completely. The solvent was removed under reduced pressure and diluted with EtOAc (20 mL). Then the mixture was washed with $NaHCO_3$ (30mL x 3), the organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The crude product was used directly for the next step without purification. The product methyl 3-bromo-6-chloro-4-fluoro-pyrrolo[2,3-b]pyridine-1-carboxylate (5 g, crude) was obtained as white solid. LCMS (ESI) m/z 309.0 $[M+H]^+$

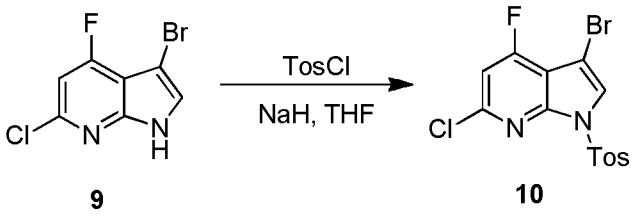
3-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine



To a solution of methyl 3-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine-1-carboxylate (5 g, 16.26 mmol, 1 *eq*) in MeOH (40 mL) was added NaOH(solved in water) (2 M, 27.03 mL, 3.32 *eq*). The mixture was stirred at 15 °C for 12 hr. LCMS showed the starting material was consumed completely. The mixture was diluted with EtOAc (30 mL), the organic phase was washed with saturated brine (30 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc= 1:0 to 5:1). TLC (Petroleum ether : EtOAc= 5:1, Rf=0.20) showed new spots

was observed. The 3-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (2 g, 7.62 mmol, 46.84% yield, 95% purity) was obtained as white solid. LCMS (ESI) m/z 369.0 $[M-TMS+H]^+$

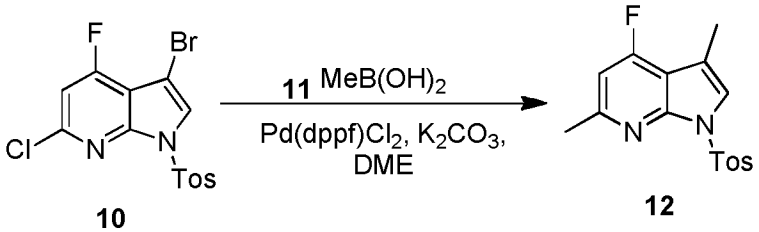
3-bromo-6-chloro-4-fluoro-1-(p-toly lsulfonyl)pyrrolo[2,3-b]pyridine



9 **10**

To a solution of 3-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (2.8 g, 11.22 mmol, 1 *eq*) in THF (40 mL) was added NaH (1.35 g, 33.67 mmol, 60% purity, 3 *eq*) at 0 °C. TosCl (3.21 g, 16.84 mmol, 1.5 *eq*) was added. The mixture was stirred at 15 °C for 12 h. LCMS showed no starting material. TLC (Petroleum ether/EtOAc=10:1, Rf= 0.50) showed no starting material and new spots was observed. The reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl. Then diluted with water (10 mL), acidified with HCl (2 M) to pH = 6. The mixture was concentrated in reduced pressure. The resulting solution was extracted with EtOAc (30 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 3-bromo-6-chloro-4-fluoro-1-(p-toly lsulfonyl)pyrrolo[2,3-b]pyridine (4.16 g, 9.28 mmol, 82.64% yield, 90% purity) was obtained as white solid. LCMS (ESI) m/z 404.9 $[M-TMS+H]^+$

4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

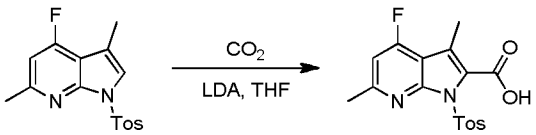


10 **12**

A mixture of 3-bromo-6-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (3.4 g, 8.42 mmol, 1 *eq*), $MeB(OH)_2$ (5.04 g, 84.23 mmol, 10 *eq*), K_2CO_3 (3.49 g, 25.27 mmol, 3 *eq*),

$Pd(dppf)Cl_2.CH_2Cl_2$ (687.86 mg, 842.31 umol, 0.1 *eq*) in DMF (50 mL). Then the mixture was stirred at 120 °C for 12 hr under N_2. LCMS showed there were no starting material and main desired compound. The reaction mixture was added to water (100 mL). The resulting solution was extracted with EtOAc (30mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.2 g, 3.58 mmol, 42.51% yield, 95% purity) was obtained as a white solid. LCMS (ESI) m/z 318.9 $[M+H]^+$

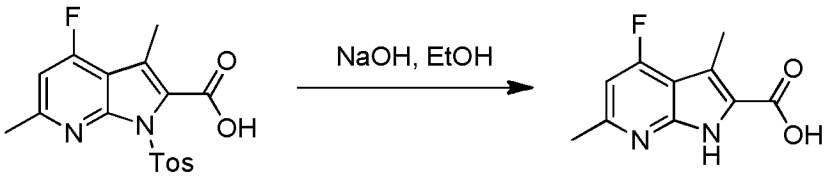
4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine-2-carboxylic acid



12 13

To a solution of 4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.1 g, 3.46 mmol, 1 *eq*) in THF (10 mL) was added LDA (2 M, 3 mL, 1.74 *eq*) under N_2 at -78 °C. The mixture was stirred at -78 °C for 1.5 h. Then the mixture was stirred at -78 °C for 0.5 h under carbon dioxide (152.06 mg, 3.46 mmol, 1 *eq*). LC-MS showed 13% of the starting material was remained. The reaction was quenched with saturated aqueous NH_4Cl (2 mL). The mixture was filtered to give product 1. The aqueous phase was acidified with saturated aqueous Na_2CO_3 to pH = 9. The mixture was washed with 20 mL x 2 of EtOAc. The mixture was acidified with HCl (2 M) to pH = 5. The mixture was filtered to give the product. The crude product was used directly for the next step without purification. The product 4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine-2-carboxylic acid (1.25 g, crude) was obtained as a yellow solid. LCMS (ESI) m/z 363.0 $[M+H]^+$

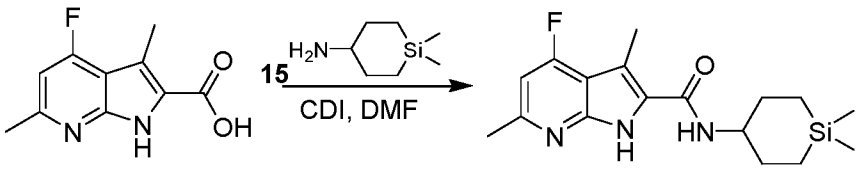
4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



13 **14**

To a solution of 4-fluoro-3,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (1 g, 2.76 mmol, 1 *eq*) in THF (10 mL) was added NaOH (solution in water) (2 M, 10 mL, 7.25 *eq*). The mixture was stirred at 30 °C for 12 h. LCMS showed no starting material and desired mass was detected. The mixture was acidified with HCl (2 M) to pH = 8 and concentrated under reduced pressure. The mixture was washed with EtOAc (20 mL) and acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (360 mg, 1.64 mmol, 59.53% yield, 95% purity) was obtained as a white solid. LCMS (ESI) m/z 208.9 $[M+H]^+$

N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



14 **MPL-209**

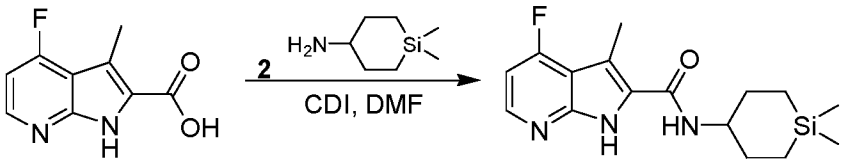
To a solution of 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 960.67 umol, 1 *eq*) and CDI (202.50 mg, 1.25 mmol, 1.3 *eq*) in DMF (2 mL). The mixture was stirred at 30 °C for 3 h. 1,1-dimethylsilinan-4-amine (178.96 mg, 1.25 mmol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 1 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (20 mL), then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 44%-74%,11min). Then lyophilized. The product N-(1,1-

dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (30.1 mg, 89.64 umol, 9.33% yield, 99.315% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 334.1 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 11.83 (br s, 1H), 7.75 (br d, *J*=7.6 Hz, 1H), 6.81 (d, *J*=11.9 Hz, 1H), 3.76 - 3.65 (m, 1H), 2.56 (s, 3H), 2.51 (br s, 3H), 2.05 - 1.96 (m, 2H), 1.63 - 1.52 (m, 2H), 0.78 (br d, *J*=14.6 Hz, 2H), 0.60 (dt, *J*=4.6, 13.7 Hz, 2H), 0.08 (s, 3H), 0.03 (s, 3H).

Example 26. MPL-210

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



1 **MPL-210**

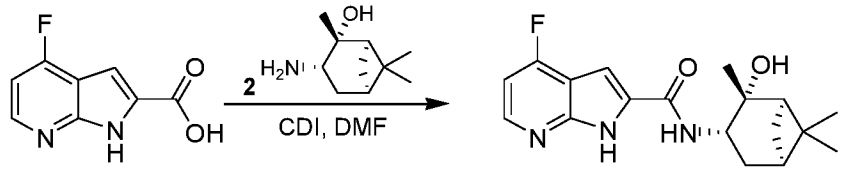
To a solution of 4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (290 mg, 1.49 mmol, 1 *eq*) in DMF (5 mL) was added CDI (290.62 mg, 1.79 mmol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Then 1,1-dimethylsilinan-4-amine (235.44 mg, 1.64 mmol, 1.1 *eq*) was added, the mixture was stirred at 30 °C further 1 hr. LC-MS showed reactant was consumed completely and desired mass was detected. The mixture was filtered; the filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water (0.225%FA)-ACN]; B%: 58%-88%,10min). LCMS showed the product was not pure enough after prep-HPLC, the product was then washed with MeCN (10mL). Filtered, the filter cake was combined with dried in lyophilizer. Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (70 mg, 219.13 umol, 14.67% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 320.0 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.93 (br s, 1 H) 8.21 (dd, *J*=7.86, 5.57 Hz, 1 H) 7.79 (br d, *J*=7.63 Hz, 1 H) 6.85 (dd, *J*=10.91, 5.26 Hz, 1 H) 3.57 - 3.69

(m, 1 H) 2.51 (s, 3 H) 1.89 - 1.99 (m, 2 H) 1.42 - 1.56 (m, 2 H) 0.70 (br d, *J*=14.65 Hz, 2 H) 0.52 (td, *J*=13.73, 4.58 Hz, 2 H) -0.10 - 0.03 (m, 6 H).

Example 27. MPL-213

Synthesis of 4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



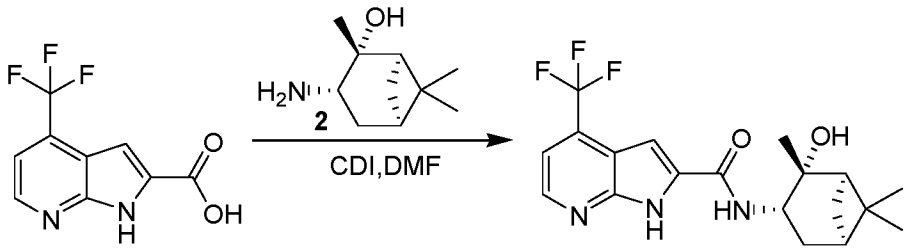
1 **MPL-213**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 277.57 umol, 1 *eq*) in DMF (2 mL) was added CDI (54.01 mg, 333.08 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Then (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (65.77 mg, 388.60 umol, 1.4 *eq*) was added. The mixture was stirred at 30 °C further 12 hr. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was filtered; the filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 44%-64%,11min). Compound 4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (53 mg, 155.36 umol, 55.97% yield, 97.138% purity) was obtained as a white solid.

LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ = ppm 12.55 (br s, 1 H), 8.32 (dd, *J*=8.22, 5.48 Hz, 1 H), 8.02 (d, *J*=8.61 Hz, 1 H), 7.26 (d, *J*=1.96 Hz, 1 H), 7.01 (dd, *J*=10.37,5.28 Hz, 1 H), 4.44 - 4.60 (m, 2 H), 2.21 - 2.30 (m, 1 H), 2.07 - 2.16 (m, 1 H), 1.89 (br d, *J*=5.48 Hz, 2 H), 1.57 - 1.70 (m, 2 H), 1.26 (s, 3 H), 1.20 (s, 3 H), 1.06 (s,3 H).

Example 28. MPL-216

Synthesis of N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-(trifluoro methyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

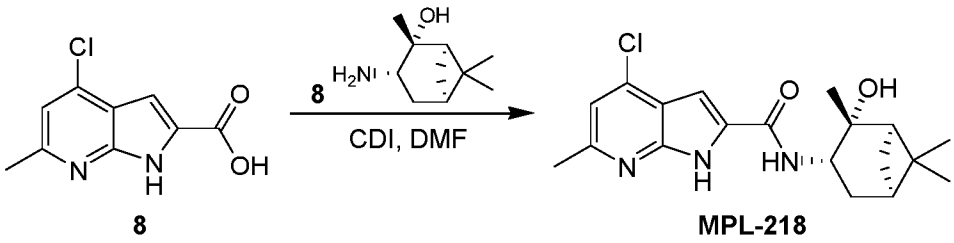


To a solution of 4-(trifluoromethyl)-1H-pyrrolo [2, 3-b] pyridine-2-carboxylic acid (150 mg, 651.77 umol, 1 *eq*) in DMF (4 mL) was added CDI (116.25 mg, 716.94 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then (1R, 2R, 3S, 5R)-3-amino-2, 6, 6-trimethyl-norpinan-2-ol (143.42 mg, 847.30 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there were main desired compound and a little starting material. Then (1R, 2R, 3S, 5R)-3-amino-2, 6, 6-trimethyl-norpinan-2-ol (0.2 eq, 22mg) was added. The mixture was stirred at 30 °C for 2 h. LCMS showed there were main desired compound and a little starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transferred in bottom flask. The residue was purified by perp. HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water (0.225%FA)-ACN];B%: 50%-79%,11min). Compound N-[(1R, 2R, 3S, 5R)-2-hydroxy-2, 6, 6-trimethyl-norpinan-3-yl]-4-(trifluoromethyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxamide (88.2 mg, 223.01 umol, 34.22% yield, 96.434% purity) was obtained as a white solid.

LCMS (ESI), m/z 382.2$[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.81 (br s, 1H), 8.55 (d, *J*=4.3 Hz, 1H), 8.23 (d, *J*=9.0 Hz, 1H), 7.49 (d, *J*=5.1 Hz, 1H), 7.40 (s, 1H), 4.62 - 4.54 (m, 1H),4.53 (s, 1H), 2.26 (br t, *J*=10.8 Hz, 1H), 2.12 (br s, 1H), 1.90 (br d, *J*=5.1 Hz, 2H), 1.71 (br dd, *J*=8.0, 13.5 Hz, 1H), 1.64 (d, *J*=9.8 Hz, 1H), 1.27 (s, 3H), 1.22(s, 3H), 1.07 (s, 3H).

Example 29. MPL-218

Synthesis of 4-chloro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-6- methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

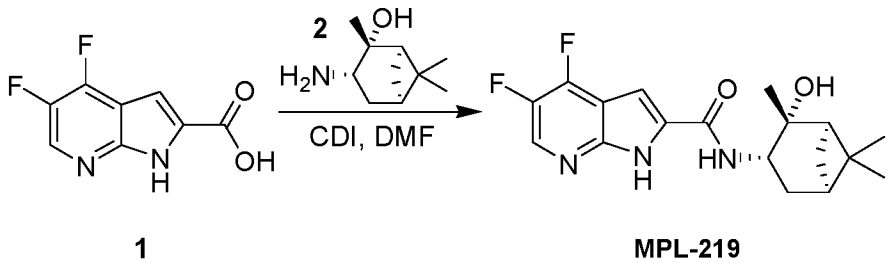


To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 237.40 umol, 1 *eq*) in DMF (2 mL) was added CDI (50.04 mg, 308.62 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Then (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (56.26 mg, 332.36 umol, 1.4 *eq*) was added. The mixture was stirred at 30 °C further 12 hr. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was filtered; the filtrate was purified by prep-HPLC column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 53%-78%,11min. Compound 4-chloro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (44 mg, 115.14 umol, 48.50% yield, 94.693% purity) was obtained as a white solid.

LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ = 12.36 (s, 1 H), 8.04 (d, *J*=9.16 Hz, 1 H), 7.24 (d, *J*=2.14 Hz, 1 H), 7.19 (s, 1 H), 4.44 - 4.63 (m, 2 H), 2.55 (s, 3 H), 2.27 (br t, *J*=11.14 Hz, 1 H), 2.10 - 2.17 (m, 1 H), 1.91 (br d, *J*=5.65 Hz, 2 H), 1.69 (dd, *J*=13.35, 7.55 Hz, 1 H), 1.63 (d, *J*=9.92 Hz, 1 H), 1.28 (s, 3 H), 1.23 (s, 3 H), 1.08 (s, 3 H).

Example 30. MPL-219

4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide

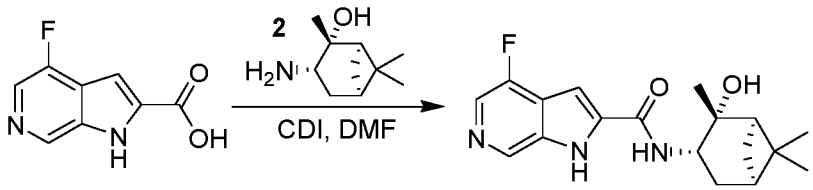


To a solution of 4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (90 mg, 454.26 umol, 1 *eq*) and CDI (88.39 mg, 545.11 umol, 1.2 *eq*) in DMF (2 mL). The mixture was stirred at 30 °C for 3 h. (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (92.27 mg, 545.11 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 1 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (20 mL), then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 43%-72%,11min),then lyophilized. The product 4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (48.2 mg, 135.85 umol, 29.91% yield, 98.468% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 349.9 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 12.68 (br s, 1H), 8.50 (dd, *J*=3.4, 9.8 Hz, 1H), 8.07 (d, *J*=9.0 Hz, 1H), 7.34 (s, 1H), 4.57 - 4.50 (m, 2H), 2.28 (br t, *J*=11.2 Hz, 1H), 2.16 - 2.09 (m, 1H), 1.90 (br d, *J*=5.8 Hz, 2H), 1.70 - 1.59 (m, 2H), 1.27 (s, 3H), 1.21 (s, 3H), 1.07 (s, 3H).

Example 31. MPL-221

4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



1 MPL-221

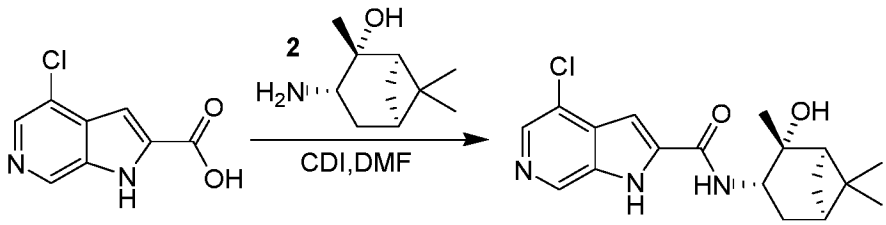
To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) and CDI (117.02 mg, 721.68 umol, 1.3 *eq*) in DMF (1.5 mL). The mixture was stirred at 30°C for 0.5 h. Then (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (122.15 mg, 721.68 umol, 1.3 *eq*) was added. The mixture was stirred at 30°C for 11.5 h. LC-MS showed most of the starting material was consumed. The reaction mixture was added to water (20 mL), then

filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product 4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (61.1 mg, 181.29 umol, 32.66% yield, 98.326% purity) was obtained as a white solid.

LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.47 (br s, 1H), 8.67 (d, *J*=2.4 Hz, 1H), 8.19 (br d, *J*=8.8 Hz, 1H), 8.09 (d, *J*=1.7 Hz, 1H), 7.41 (s, 1H), 4.61 - 4.49 (m, 2H), 2.34 - 2.25 (m, 1H), 2.16 - 2.09 (m, 1H), 1.90 (br d, *J*=5.4 Hz, 2H), 1.75 - 1.60 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H), 1.07 (s, 3H).

Example 32. MPL-222

Synthesis of 4-chloro-N-[(1R, 2R, 3S, 5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-Pyrrolo [2,3-c]pyridine-2-carboxamide



To a solution of 4-chloro-1H-pyrrolo [2, 3-c] pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) DMF (1.5 mL) was added CDI (45.36 mg, 279.77 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then (1R, 2R, 3S, 5R)-3-amino-2, 6, 6-trimethyl-norpinan-2-ol (45.20 mg, 267.05 umol, 1.05 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there was no starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transfered in bottom flask. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water (0.225%FA)-ACN];B%:25%-55%,11min)Compound 4-chloro-N-[(1R,2R,3S,5R)-2-hydroxy

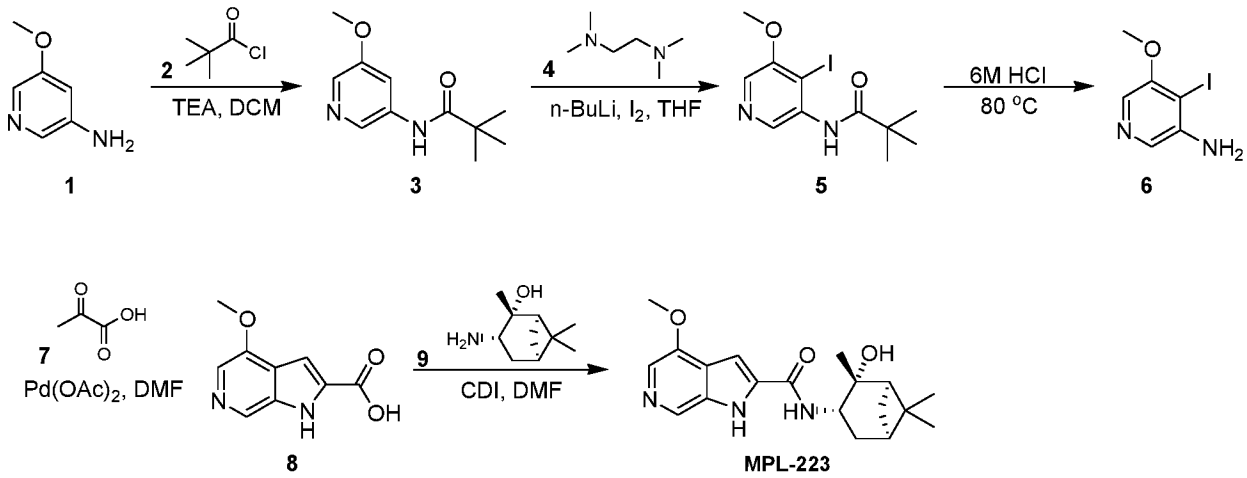
-2, 6, 6-trimethyl-norpinan-3-yl]-1H-pyrrolo [2,3-c]pyridine-2-carboxamide (33 mg, 94.72 umol, 37.24% yield, 99.840% purity) was obtained as a white solid.

LCMS (ESI), m/z 348.0[M+H]$^+$

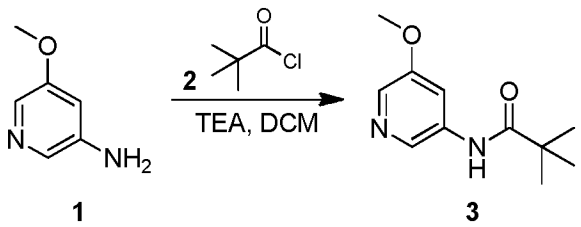
^{1}H NMR (500MHz, CDCl3) δ = 10.58 (br s, 1H), 8.85 (s, 1H), 8.28 (s, 1H), 7.53 (br d, *J*=7.5 Hz, 1H), 7.01 (s, 1H), 4.61 - 4.55 (m, 1H), 2.78 -2.71 (m, 1H), 2.37 - 2.28 (m, 1H), 2.11 - 2.05 (m, 2H), 1.68 (br dd, *J*=6.2, 13.0 Hz, 1H), 1.49 (d, *J*=10.5 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.16 (s, 3H).

Example 33. MPL-223

Scheme



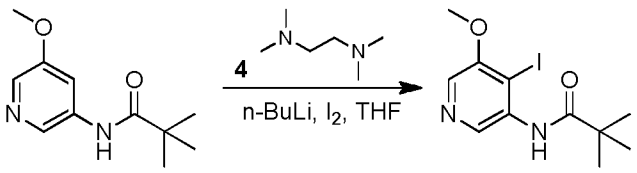
Synthesis of N-(5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide



To an ice-cooled solution of 5-methoxypyridin-3-amine (10 g, 80.55 mmol, 1 *eq*) in CH_2Cl_2 (100 mL) was added TEA (24.45 g, 241.66 mmol, 33.64 mL, 3 *eq*). Then 2,2-dimethylpropanoyl chloride (10.68 g, 88.61 mmol, 10.90 mL, 1.1 *eq*) was added at 0 °C. The mixture was allowed

warm to 10 °C gradually and stirred 12 hr. TLC (Petroleum ether:EtOAc = 1:1, Rf = 0.3) indicated the starting material was consumed completely, and one major new sport with lower polarity was detected. Water (100mL) was added to the mixture, followed by CH_2Cl_2 (200mL). The separated organic layer was washed with brine (Sat. 200mL) then dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford crude product which was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~80% EtOAc/Petroleum ether gradient at 60 mL/min). Compound N-(5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide (15 g, 68.43 mmol, 84.94% yield, 95% purity) was obtained as a white solid.

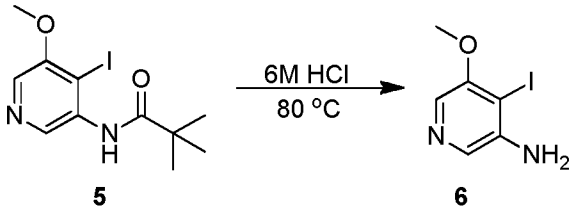
Synthesis of N-(4-iodo-5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide



3 5

To a solution of N-(5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide (14 g, 67.22 mmol, 1 *eq*) in dried THF (150mL) was added TMEDA (25.00 g, 215.12 mmol, 32.46 mL, 3.2 *eq*). The solution was cooled to -78 °C then n-BuLi (2.5 M, 86.05 mL, 3.2 *eq*) was added under N_2 (maintain temperature below - 60 °C). The mixture was stirred at -78 °C for 3 hr. I_2 (27.30 g, 107.56 mmol, 21.67 mL, 1.6 *eq*) in dried THF (80mL) was added dropwise (maintain temperature below - 60 °C). The mixture was allowed warm to 10 °C after addition and stirred further 12 hr. TLC (Petroleum ether:EtOAc = 1:1, Rf = 0.4) indicated starting material was consumed completely and one new spot formed. Na_2SO_3 (Sat. in water, 100mL) was added to the mixture, THF was removed under reduced pressure. The product was extracted with CH_2Cl_2 (150mL x 3), the combined organic layer was dried over Na_2SO_4. Filtered, the filtrate was concentrated under reduced pressure at 40 °C until 100mL solvent left. The product was recrystallized in CH_2Cl_2, filtered to give the product. Compound N-(4-iodo-5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide (19.2 g, 54.59 mmol, 81.20% yield, 95% purity) was obtained as a pink solid.

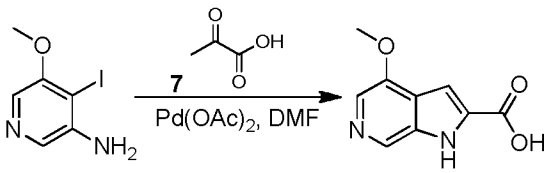
Synthesis of 4-iodo-5-methoxy-pyridin-3-amine



5 6

The reactant N-(4-iodo-5-methoxy-3-pyridyl)-2,2-dimethyl-propanamide (12 g, 35.91 mmol, 1 *eq*) was dissolved in HCl (6 M, 150 mL, 25.06 *eq*). The mixture was stirred at 80 °C for 12 hr. TLC (Petroleum ether: EtOAc = 1:1, Rf = 0.3) indicated the starting material was consumed completely and one new spot with larger polarity was detected. NaOH (6M, in water) was added to adjust pH to 8. The product was extracted with EtOAc (50mL x 4), the combined organic layer was washed with brine (50mL), dried over Na_2SO_4. Filtered and concentrated under reduced pressure to afford the product. Compound 4-iodo-5-methoxy-pyridin-3-amine (8.4 g, 31.92 mmol, 88.87% yield, 95% purity) was obtained as a yellow solid.

Synthesis of 4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

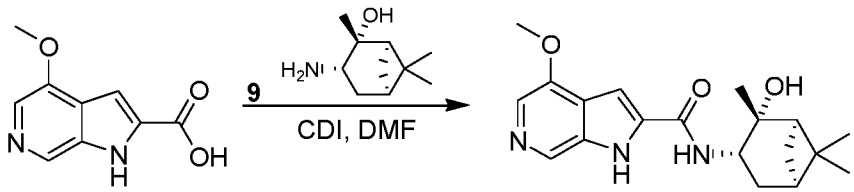


6 8

To a mixture of 4-iodo-5-methoxy-pyridin-3-amine (3 g, 12.00 mmol, 1 *eq*), 2-oxopropanoic acid (2.26 g, 18.00 mmol, 1.81 mL, 1.5 *eq*) and DABCO (2.69 g, 24.00 mmol, 2.64 mL, 2 *eq*) was added DMF (100 mL). Then $Pd(OAc)_2$ (538.74 mg, 2.40 mmol, 0.2 *eq*) was added under N_2. The mixture was stirred at 115 °C for 4 hr. LCMS showed Reactant was consumed completely and one main peak with desired mass was detected. DMF was removed under reduced pressure by oil pump. Toluene (60mL) was added to the mixture and washed in ultrasound for 15 min. Then toluene was pooled off carefully while the brown solid was remained. The solid was redissolved in water (50mL), the turbid liquid was washed in ultrasound while HCl (6M, in water) was added dropwise to adjust pH to 5. Filtered, the filter cake was washed with MeCN (20mL) in ultrasound (30 min), filtered to afford the product.

Compound 4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (2.03 g, 10.04 mmol, 83.64% yield, 95% purity) was obtained as a brown solid. LCMS (ESI) m/z 193.1 $[M+H]^+$

Synthesis of N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-methoxy- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide

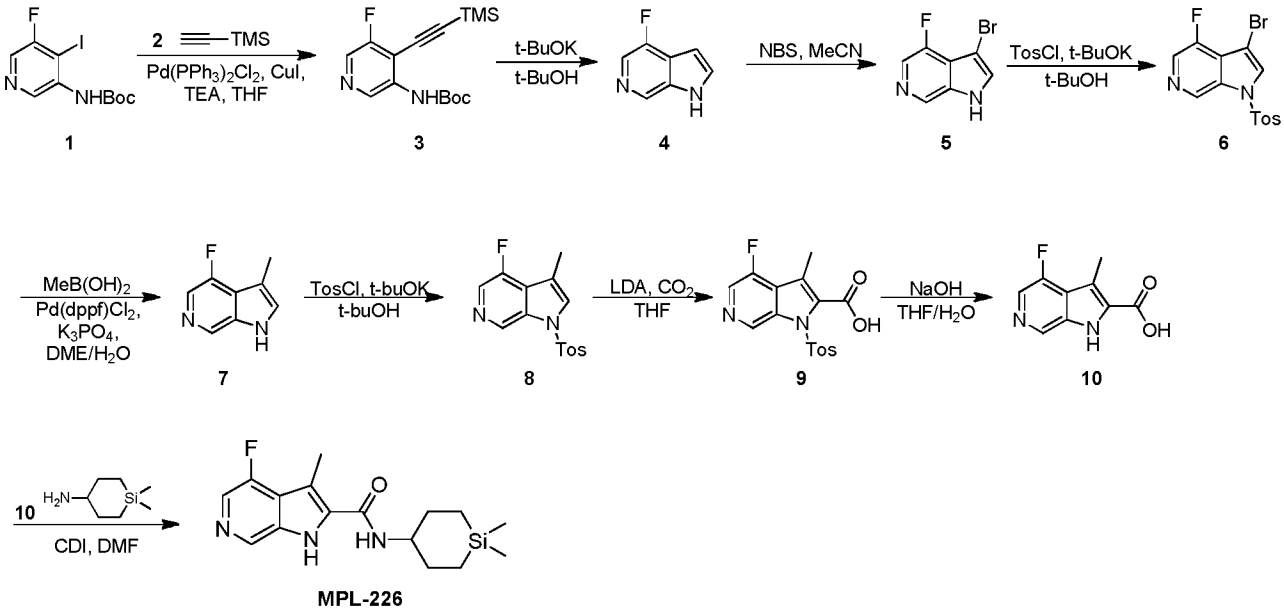


To a solution of 4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 260.18 umol, 1 *eq*) in DMF (1 mL) was added CDI (54.85 mg, 338.24 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Then (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (57.25 mg, 338.24 umol, 1.3 *eq*) was added, the mixture was stirred at 30 °C for 1hr. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was filtered, the filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 27%-57%,11min). Compound N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6- trimethyl-norpinan-3-yl]-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (88 mg, 244.89 umol, 94.12% yield, 95.569% purity) was obtained as a white solid.

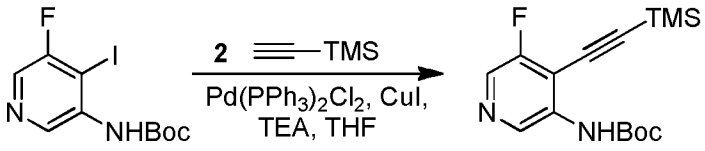
LCMS (ESI) m/z 344.2 $[M+H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.48 (br s, 1 H), 8.57 (br s, 1 H), 8.18 (br d, *J*=9.00 Hz, 1 H), 7.89 (br s, 1 H), 7.45 (s, 1 H), 4.48 - 4.61 (m, 2 H), 4.04 (s, 3H), 2.25 - 2.33 (m, 1 H), 2.10 - 2.18 (m, 1 H), 1.91 (br d, *J*=5.80 Hz, 2 H), 1.71 (br dd, *J*=13.43, 7.48 Hz, 1 H), 1.64 (d, *J*=9.92 Hz, 1 H), 1.28 (s, 3 H) 1.26 - 1.26 (m, 1 H), 1.24 (s, 3 H), 1.08 (s, 3 H).

Example 34. MPL-226

Scheme

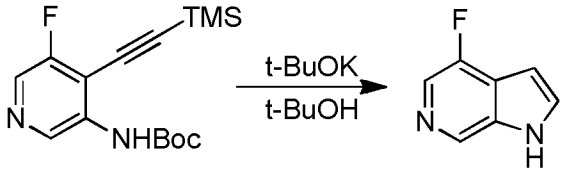


tert-butyl N-[5-fluoro-4-(2-trimethylsilylethynyl)-3-pyridyl]carbamate



To a solution of tert-butyl N-(5-fluoro-4-iodo-3-pyridyl)carbamate (20 g, 59.15 mmol, 1 *eq*) $Pd(PPh_3)_2Cl_2$ (2.08 g, 2.96 mmol, 0.05 *eq*) ,CuI (3.38 g, 17.75 mmol, 0.3 *eq*) in THF (200 mL) was added ethynyl(trimethyl)silane (58.10 g, 591.51 mmol, 81.94 mL, 10 *eq*) and TEA (17.96 g, 177.45 mmol, 24.70 mL, 3 *eq*) under N_2. The mixture was stirred at 30 °C for 5 hr under N_2. LCMS showed 8% of the starting material still remaining and the desired compound as the main product. The mixture was concentrated in reduced pressure. The residue was diluted with H_2O (100 mL). The aqueous phase was extracted with EtOAc (100 mL x 3). The combined organic phase was washed with saturated NaCl (100 mL x 2). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product tert-butyl N-[5-fluoro-4-(2-trimethylsilylethynyl)-3-pyridyl]carbamate (16 g, 51.88 mmol, 87.70% yield) was obtained as a yellow solid. LCMS (ESI) m/z 309.1 $[M+H]^+$

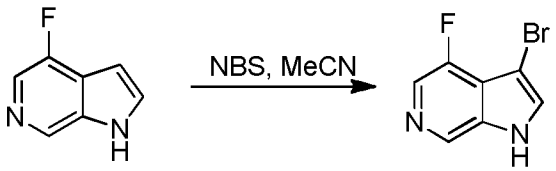
4-fluoro-1H-pyrrolo[2,3-c]pyridine



3 **4**

To a solution of tert-butyl N-[5-fluoro-4-(2-trimethylsilylethynyl)-3-pyridyl]carbamate (16 g, 51.88 mmol, 1 *eq*) in t-BuOH (200 mL) was added t-BuOK (17.46 g, 155.63 mmol, 3 *eq*). The mixture was stirred at 80 °C for 9 h. LCMS showed desired compound mass was detected. TLC (Petroleum ether: EtOAc=1:1) showed most of the starting material 1 was consumed and new spots was observed. The mixture was concentrated in reduced pressure. The mixture was diluted with EtOAc (50 mL). The filtrate was washed with water (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 1:1). The crude product 4-fluoro-1H-pyrrolo[2,3-c]pyridine (4.7 g, 32.80 mmol, 63.23% yield, 95% purity) was obtained as a yellow solid. LCMS (ESI) m/z $[M+H]^+$

3-bromo-4-fluoro-1H-pyrrolo[2,3-c]pyridine

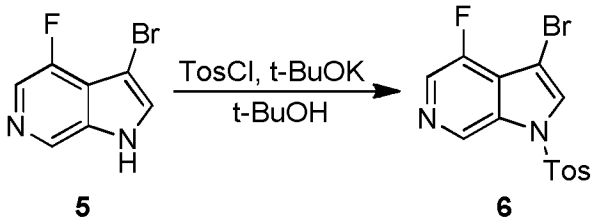


4 **5**

To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine (4.2 g, 30.85 mmol, 1 *eq*) in MeCN (50 mL) was added NBS (8 g, 44.95 mmol, 1.46 *eq*) at 0 °C. The mixture was stirred at 30 °C for 12 h. LCMS showed desired mass was detected. TLC (Petroleum ether/EtOAc=3:1, Rf=0.10) showed new spots was observed. The crude product was used directly for the next step without purification. The product 3-bromo-4-fluoro-1H-pyrrolo[2,3-c]pyridine (6 g, crude) was obtained as yellow solid.

LCMS (ESI) m/z 216.9 $[M+H]^+$

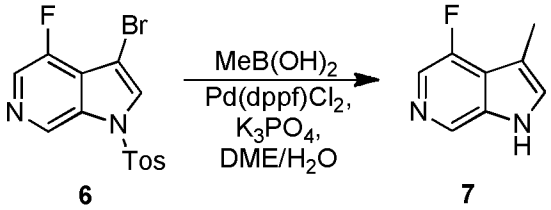
3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine



5 **6**

To a solution of 3-bromo-4-fluoro-1H-pyrrolo[2,3-c]pyridine (6 g, 27.90 mmol, 1 *eq*) in t-BuOH (10 mL) was added t-BuOK (9.39 g, 83.71 mmol, 3 *eq*) and TosCl (6.92 g, 36.28 mmol, 1.3 *eq*). The mixture was stirred at 25 °C for 12 h. LC-MS showed the starting material was consumed completely. The mixture was concentrated in reduced pressure. The mixture was diluted with EtOAc (50 mL). The filtrate was washed with water (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 5:1). The product 3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (3.8 g, 9.78 mmol, 35.04% yield, 95% purity) was obtained as a yellow solid. LCMS (ESI) m/z 369.0 $[M\text{-}TMS+H]^+$

4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine

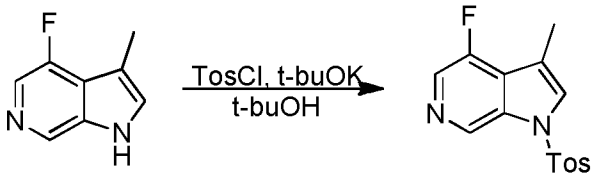


6 **7**

A mixture of 3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (3.8 g, 10.29 mmol, 1 *eq*), $MeB(OH)_2$ (6.16 g, 102.92 mmol, 10 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (840.51 mg, 1.03 mmol, 0.1 *eq*), K_2CO_3 (4.27 g, 30.88 mmol, 3 *eq*) in DMF (40 mL). Then the mixture was stirred at 120 °C for 12 hr under N_2. LCMS showed there were no starting material and main desired compound. The reaction mixture was added to water (100 mL). The resulting solution was extracted with EtOAc (30mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 4-fluoro-3-methyl-1H-pyrrolo[2,3-

c]pyridine (2 g, 5.33 mmol, 51.77% yield, 40% purity) was obtained as a yellow solid. LCMS (ESI) m/z 137.1 $[M-TMS+H]^+$

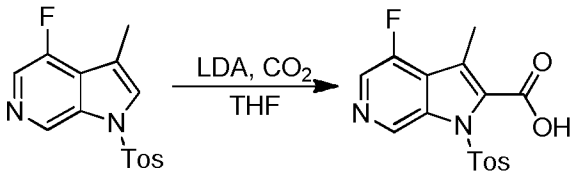
4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine



7 **8**

To a solution of 4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine (2 g, 13.32 mmol, 1 *eq*) in t-BuOH (15 mL) was added t-BuOK (3.74 g, 33.30 mmol, 2.5 *eq*) and TosCl (3.30 g, 17.32 mmol, 1.3 *eq*). The reaction was stirred at 30 °C for 12 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (100 mL). The resulting solution was extracted with EtOAc (30mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (750 mg, 2.46 mmol, 18.50% yield) was obtained as white solid. LCMS (ESI) m/z 305.1 $[M+H]^+$

4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid

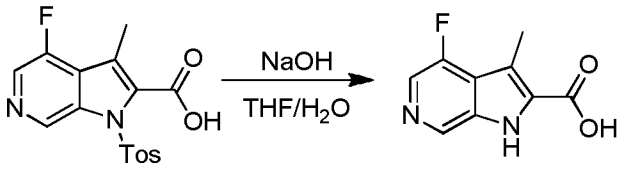


8 **9**

To a solution of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (750 mg, 2.46 mmol, 1 *eq*) in THF (10 mL) was added LDA (2 M, 2.46 mL, 2 *eq*) under N_2 at -78 °C. The mixture was stirred at-78 °C for 2 h. Then the mixture was stirred at -78 °C for 1 h under CO_2 (15 psi). LC-MS showed 3% of the starting material was remained. The reaction was quenched with saturated aqueous NH_4Cl (2 mL). The aqueous phase was adjusted with saturated aqueous Na_2CO_3 to pH = 9. The mixture was washed with 20 mL x 2 of EtOAc. The mixture was

acidified with HCl (2 M) to pH = 5. The mixture was filtered to give the product. The crude product was used directly for the next step without purification. The product 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid (858.45 g, crude) was obtained as a yellow solid. LCMS (ESI) m/z 349.1 $[M+H]^+$

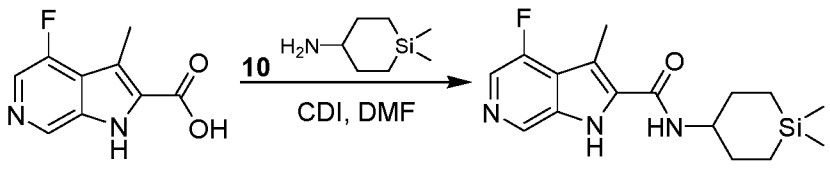
4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



9 **10**

To a solution of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid (961.29 mg, 2.76 mmol, 1 *eq*) in THF (10 mL) was added NaOH (solution in water) (2 M, 10 mL, 7.25 *eq*). The mixture was stirred at 30 °C for 12 h. LCMS showed no starting material and desired mass was detected. The mixture was acidified with HCl (2 M) to pH = 8 and concentrated under reduced pressure. The mixture was washed with EtOAc (20 mL) and acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product 4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (430 mg, 1.99 mmol, 72.23% yield, 90% purity) was obtained as a white solid. LCMS (ESI) m/z 195.0 $[M+H]^+$

N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine -2-carboxamide



10 **MPL-226**

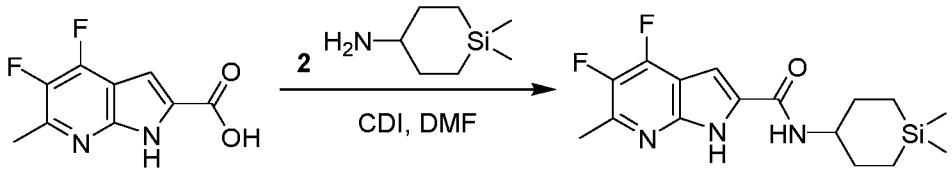
To a solution of 4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (200 mg, 1.03 mmol, 1 *eq*) and CDI (200.43 mg, 1.24 mmol, 1.2 *eq*) in DMF (2.5 mL). The mixture was stirred at 30 °C for 3 h. 1,1-dimethylsilinan-4-amine (177.13 mg, 1.24 mmol, 1.2 *eq*) was added.

The mixture was stirred at 30 °C for 1 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (20 mL), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The crude product was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.05%HCl)-ACN];B%: 28%-48%,10min),then lyophilized to give the product. The product N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (74.8 mg, 216.26 umol, 20.99% yield, 92.359% purity) was obtained as a white solid.

LCMS (ESI) m/z 320.0 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 13.52 (br s, 1H), 8.99 (s, 1H), 8.58 (br d, *J*=7.8 Hz, 1H), 8.46 (d, *J*=4.4 Hz, 1H), 3.82 - 3.69 (m, 1H), 2.60 (s, 3H), 2.07 - 2.00 (m, 2H), 1.69 - 1.60 (m, 2H), 0.80 (br d, *J*=14.5 Hz, 2H), 0.62 (dt, *J*=4.8, 13.8 Hz, 2H), 0.08 (s, 3H), 0.04 (s, 3H).

Example 35. MPL-229

Synthesis of N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b] pyridine-2-carboxamide



MPL-229

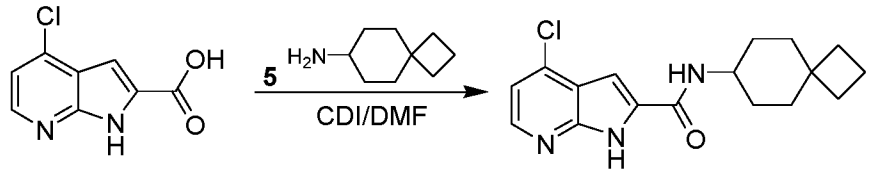
To a solution of 4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b] pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (33.63 mg, 207.40 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 1, 1-dimethylsilinan-4-amine (29.72 mg, 207.40 umol, 1.1 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there were main desired compound and a little starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transferred in bottom flask. The crude product was purified by prep-TLC (SiO_2, Petroleum ether: EtOAc =5:1). Compound N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b]

pyridine-2- carboxamide (30 mg, 88.39 umol, 46.88% yield, 99.423% purity) was obtained as a white solid.

LCMS (ESI), m/z 338.0[M+H]$^+$; ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.55 (br s, 1H), 6.80 (s, 1H), 6.04 (br d, *J*=8.2 Hz, 1H), 3.91 (br d, *J*=8.2 Hz, 1H), 2.63 (d, *J*=3.1 Hz, 3H), 2.18(br d, *J*=10.2 Hz, 2H), 1.59 - 1.53 (m, 2H), 0.83 - 0.68 (m, 4H), 0.10 (s, 3H), 0.06 (s, 3H).

Example 36. MPL-001

Synthesis of 4-chloro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



4 **MPL-001**

To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (190 mg, 966.48 umol, 1 *eq*) in DMF (4 mL) was added CDI (188.06 mg, 1.16 mmol, 1.2 *eq*) and spiro[3.5]nonan-7-amine (188.40 mg, 1.35 mmol, 1.4 *eq*). The mixture was stirred at 30 °C for 12 hr. LCMS showed there were no starting material and main desired compound. There was much precipitation. The mixture was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was washed with H_2O (10 mL). The solid was diluted with CH_3CN(1 mL) and H_2O (10 mL), then lyophilized. Compound 4-chloro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (140 mg, 435.75 umol, 45.09% yield, 98.92% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR. LCMS (ESI) m/z 318.1 [M+H]$^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 12.48 (br s, 1H), 8.40 - 8.31 (m, 1H), 8.27 (d, *J*=5.0 Hz, 1H), 7.29 - 7.22 (m, 2H), 3.73 (br s, 1H), 1.88 - 1.81 (m, 2H), 1.80 - 1.73 (m, 4H), 1.70 (br d, *J*=7.8 Hz, 4H), 1.43 - 1.28 (m, 4H).

Example 37. MPL-002

Synthesis of 4-fluoro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

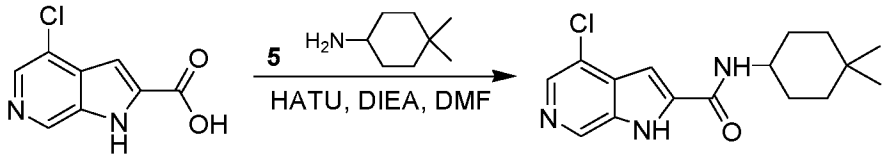
1 MPL-002

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 1.11 mmol, 1 *eq*) in DMF (2 mL) was added CDI (234.04 mg, 1.44 mmol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. spiro[3.5]nonan-7-amine (200.97 mg, 1.44 mmol, 1.3 *eq*) was added and the reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was delivered without further purification. Compound 4-fluoro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (210 mg, 674.76 umol, 60.77% yield, 96.83% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 302.1 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ = 12.43 (br s, 1H), 8.34 - 8.18 (m, 1H), 8.34 - 8.18 (m, 1H), 7.21 (s, 1H), 6.97 (dd, *J*=5.3, 10.1 Hz, 1H), 3.71 (br s, 1H), 1.84- 1.63 (m, 10H), 1.40 - 1.26 (m, 1H), 1.40 - 1.26 (m, 1H), 1.40 - 1.23 (m, 2H).

Example 38. MPL-003

Synthesis of 4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide



4 MPL-003

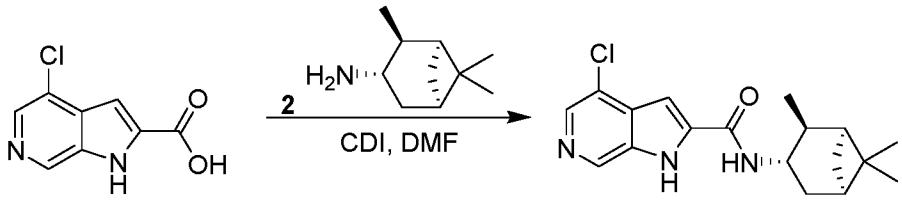
To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (800 mg, 4.07 mmol, 1 *eq*) in DMF (8 mL) was added CDI (989.77 mg, 6.10 mmol, 1.5 *eq*), the mixture was stirred at 30 °C for 2.5h, then 4,4-dimethylcyclohexanamine (776.60 mg, 6.10 mmol, 1.5 *eq*) was added. The mixture was stirred at 30 °C for another 0.5 h. LC-MS showed 20 % of the starting material

4 was remained and one main peak with desired mass was detected. The mixture was added to water (100mL), filtered and the filter cake was washed with 20 mL x 3 of Petroleum ether, dried under reduced pressure to give the product. The product 4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (692.4 mg, 2.24 mmol, 55.14% yield, 99.104% purity) was obtained as white solid.

LCMS (ESI) m/z 306.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.43 (br s, 1H), 8.72 (s, 1H), 8.59 (br d, *J*=7.6 Hz, 1H), 8.18 (s, 1H), 7.33 (s, 1H), 3.76 (br d, *J*=6.6 Hz, 1H), 1.67 (br d, *J*=10.3 Hz, 2H), 1.60 - 1.50 (m, 2H), 1.45 - 1.37 (m, 2H), 1.34 - 1.24 (m, 2H), 0.94 (br d, *J*=9.0 Hz, 6H).

Example 39. MPL-006

Synthesis of 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]Pyridine -2-carboxamide

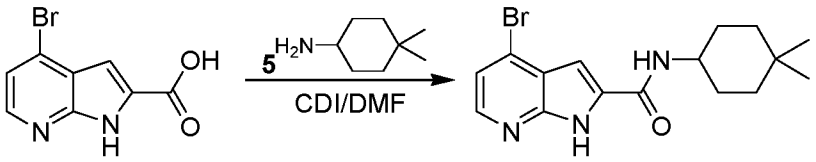


To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (250 mg, 1.27 mmol, 1 *eq*) in DMF (3 mL) was added CDI (268.06 mg, 1.65 mmol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (292.35 mg, 1.91 mmol, 1.5 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there was no starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc(30 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether ： EtOAc = 1:1). Compound 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (259 mg, 775.07 umol, 60.95% yield, 99.305% purity) was obtained as a white solid.

LCMS (ESI), m/z 331.15[M+H]$^+$; ^{1}H NMR (400MHz, DMSO-d$_6$) δ = 12.46 (br s, 1H), 8.74 (s, 1H), 8.71 (br d, *J*=8.6 Hz, 1H), 8.19 (s, 1H), 7.39 (s, 1H), 4.46 - 4.35 (m, 1H), 2.48 - 2.35 (m, 2H), 2.10 (br t, *J*=7.2 Hz, 1H), 2.01 - 1.92 (m, 1H), 1.83 (br t, *J*=5.1 Hz, 1H), 1.72 (br dd, *J*=6.4, 11.7 Hz, 1H), 1.27 - 1.20 (m, 4H), 1.11 - 1.05 (m, 6H).

Example 40. MPL-007

Synthesis of 4-bromo-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



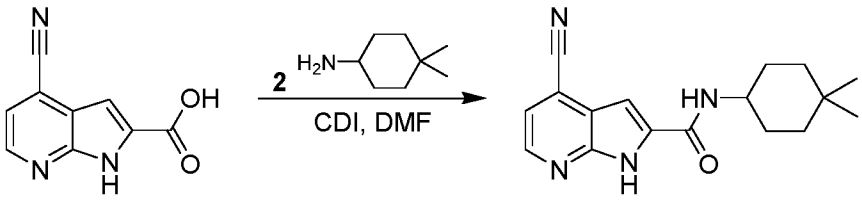
4 **MPL-007**

To a solution of 4-bromo-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid(2.00 g, 8.30 mmol, 1 *eq*) and CDI(2.02 g, 12.45 mmol, 1.5 *eq*) in DMF(20 mL), the mixture was stirred at 25 °C for 30 min, then 4,4-dimethylcyclohexanamine(1.58 g, 12.45 mmol, 1.5 *eq*) was added, the mixture was stirred at 25 °C for 0.5 h under N_2. LC-MS showed the starting material 4 was consumed completely and one main peak with desired mass was detected. The mixture was added to a solution of LiCl (300ml, 3%) and filtered. The filter cake was washed with 50 mL of water, dried under reduced pressure to give product. The product 4-bromo-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide (2.24 g, 6.40 mmol, 77.14% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 352.1 [M+H]$^+$; ^{1}H NMR (400MHz, DMSO-δ$_6$) δ = 12.48 (br s, 1H), 8.42 (br d, *J* = 7.6 Hz, 1H), 8.18 (br d, *J* = 4.9 Hz, 1H), 7.40 (br d, *J* = 4.9 Hz, 1H), 7.20 (s, 1H), 3.73 (br d, *J* = 7.8 Hz, 1H), 1.67 (br d, *J* = 10.7 Hz, 2H), 1.59 - 1.50 (m, 2H), 1.41 (br d, *J* = 12.5 Hz, 2H), 1.33 - 1.24 (m, 2H), 0.94 (br d, *J* = 11.0 Hz, 6H).

Example 41. MPL-008

Synthesis of 4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



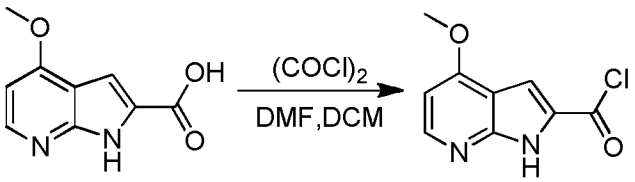
1 MPL-008

To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (500 mg, 2.67 mmol, 1 *eq*) in DMF (8 mL) was added CDI (563.15 mg, 3.47 mmol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. 4,4-dimethylcyclohexanamine (441.87 mg, 3.47 mmol, 1.3 *eq*) was added and the reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (50 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was delivered without further purification. Compound 4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (520 mg, 1.74 mmol, 65.29% yield, 99.41% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 297.1 $[M+H]^+$; 1H NMR (500MHz, DMSO-d_6) δ = 12.87 (br s, 1H), 8.54 - 8.50 (m, 1H), 8.54 - 8.50 (m, 1H), 7.65 (d, J=4.9 Hz, 1H), 7.43 (s, 1H), 3.81 - 3.71 (m, 1H), 1.69(br dd, J=3.6, 13.0 Hz, 2H), 1.61 - 1.50 (m, 2H), 1.43 (br d, J=12.5 Hz, 2H), 1.34 - 1.26 (m, 2H), 0.95 (d, J=11.1 Hz, 6H).

Example 42. MPL-009

Synthesis of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride

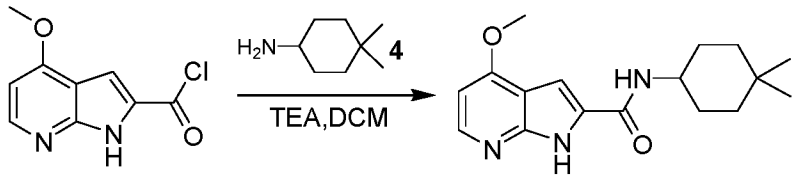


2 3

To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (300 mg, 1.56 mmol, 1 *eq*) in DCM (10 mL) was added DMF (5.71 mg, 78.06 umol, 6.01 uL, 0.05 *eq*) and $(COCl)_2$

(2.90 g, 22.85 mmol, 2 mL, 14.64 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed the starting metarial 2 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was directly used in next step without any purification. Compound 4-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carbonyl chloride (300 mg, 1.35 mmol, 86.68% yield, 95% purity) was obtained as a white solid. LCMS (ESI) m/z 207.1 $[M+H]^+$

Synthesis of N-(4,4-dimethylcyclohexyl)-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2- carboxamide

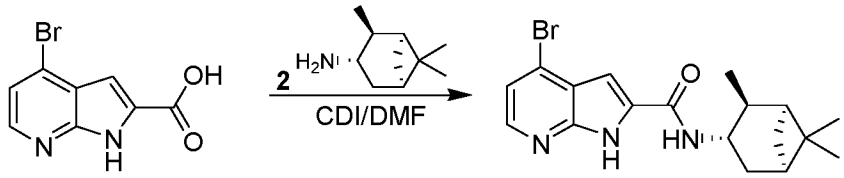


To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (300 mg, 1.42 mmol, 1 *eq*) in DCM (8 mL) was added TEA (288.27 mg, 2.85 mmol, 396.52 uL, 2 *eq*) and 4,4-dimethylcyclohexanamine (181.22 mg, 1.42 mmol, 1 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed the starting material 3 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was purified by column chromatography (SiO_2, **Petroleum ether : EtOAc = 10 : 1** to 0 **: 1**). Compound N-(4,4-dimethylcyclohexyl)-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (85 mg, 282.03 umol, 19.80% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 302.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.97 (br s, 1H), 8.19 (d, *J* = 5.5 Hz, 1H), 8.13 (br d, J = 7.9 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 6.68 (d, *J* = 5.6 Hz, 1H), 3.97 (s,3H), 3.78 - 3.66 (m, 1H), 1.73 - 1.63 (m, 2H), 1.59 - 1.37 (m, 4H), 1.28 (dt, *J* = 3.7, 13.2 Hz, 2H), 0.94 (d, *J* = 7.8 Hz, 6H).

Example 43. MPL-012

Synthesis of 4-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



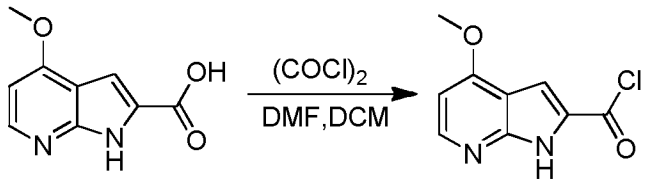
1 MPL-012

To a solution of 4-bromo-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (2.00 g, 8.30 mmol, 1 *eq*) and CDI (2.02 g, 12.45 mmol, 1.5 *eq*) in DMF (20 mL) the mixture was stirred at 25 °C for 30 min, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (1.53 g, 9.96 mmol, 1.2 *eq*) was added, the mixture was stirred at 25 °C for 0.5 h under N_2. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was added to a solution of LiCl (300ml, 3%) and filtered, the filter cake was washed with 50 mL of water, dried under reduced pressure to give the product. The product 4-bromo-N-[(1S,2S,3S,5R)-2,6,6 -trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (1.85 g, 4.74 mmol, 57.09% yield, 96.464% purity) was obtained as white solid.

LCMS (ESI) m/z 377.9 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.52 (br s, 1H), 8.55 (br d, J = 8.4 Hz, 1H), 8.19 (br d, J = 5.0 Hz, 1H), 7.41 (br d, J = 5.0 Hz, 1H), 7.24 (s, 1H), 4.38 (br s, 1H), 2.47 - 2.39 (m, 2H), 2.08 (br t, J = 7.0 Hz, 1H), 1.95 (br s, 1H), 1.82 (br d, J = 5.2 Hz, 1H), 1.71 (br dd, J = 5.4, 12.7 Hz, 1H), 1.25 - 1.18 (m, 4H), 1.10 - 1.04 (m, 6H).

Example 44. MPL-014

Synthesis of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride

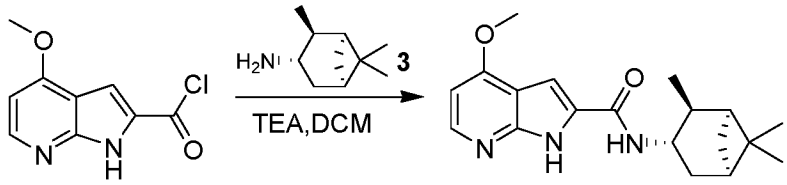


1 2

To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (300 mg, 1.56 mmol, 1 *eq*) in DCM (10 mL) was added DMF (5.71 mg, 78.06 umol, 6.01 uL, 0.05 *eq*) and $(COCl)_2$ (2.90 g, 22.85 mmol, 2 mL, 14.64 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed

the starting material 1 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was directly used in next step without any purification. Compound 4-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carbonyl chloride (300 mg, 1.35 mmol, 86.68% yield, 95% purity) was obtained as a white solid.

Synthesis of 4-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide

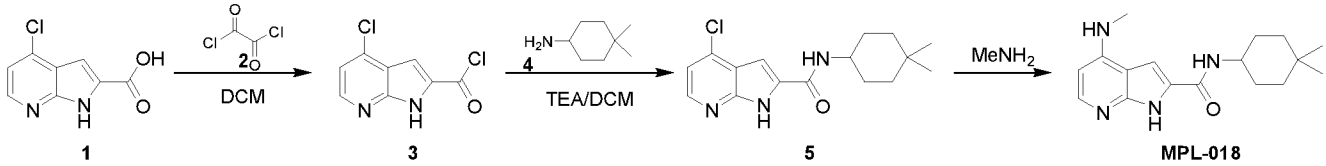


2 **MPL-014**

To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (300 mg, 1.42 mmol, 1 *eq*) in DCM (8 mL) was added TEA (288.27 mg, 2.85 mmol, 396.52 uL, 2 *eq*) and (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (174.65 mg, 1.14 mmol, 0.8 *eq*) was added. The mixture was stirred at 25 °C for 2 hrs. LCMS showed the starting material 2 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 10 : 1 to 0 : 1). Compound 4-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]- 1H-pyrrolo[2,3-b] pyridine-2-carboxamide (100 mg, 305.42 umol, 21.44% yield, 100% purity) was obtained as a white solid. LCMS (ESI) m/z 328.2 $[M+H]^+$

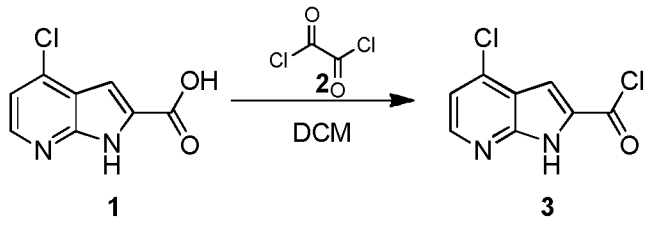
Example 45. MPL-018

Scheme



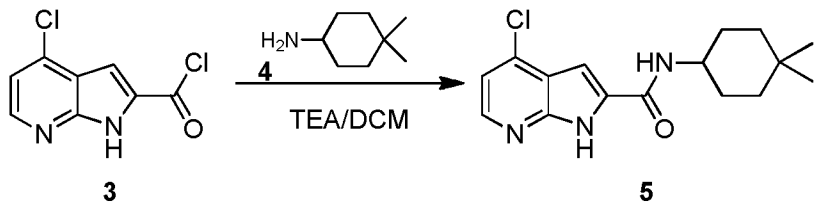
1 **3** **5** **MPL-018**

Ethyl 2-methyl-4H-pyrrolo[2,3-d]thiazole-5-carboxylate



To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100.00 mg, 508.67 umol, 1 *eq*) in DCM (5 mL) was added oxalyl dichloride (645.64 mg, 5.09 mmol, 445.27 uL, 10 *eq*) and DMF (1.12 mg, 15.26 umol, 1.17 uL, 0.03 *eq*) under N_2, the mixture was stirred at 80 °C for 12 hrs. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The crude product 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (109 mg, 506.89 umol, 99.65% yield) was obtained as yellow solid and used directly for the next step without purification.

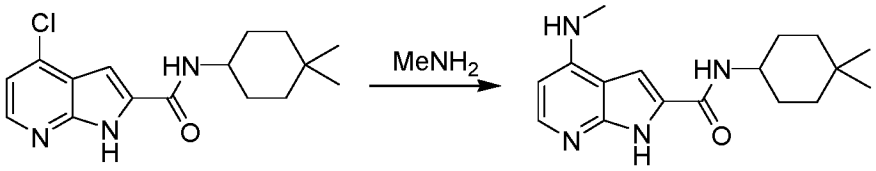
Synthesis of 4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (109 mg, 506.89 umol, 1 *eq*) in DCM (3 mL) was added 4,4-dimethylcyclohexanamine (161.23 mg, 1.27 mmol, 2.5 *eq*) and TEA (128.23 mg, 1.27 mmol, 176.38 uL, 2.5 *eq*), the mixture was stirred at 25 °C for 0.5 hr under N_2. TLC and LC-MS showed the starting material 3 was consumed completely and one main peak with desired mass was detected. The mixture was diluted with DCM: MeOH (30 mL) and washed with brine(30 mL), then extracted with DCM: MeOH (30 mL **x** 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 100:1). The product 4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-

carboxamide (110.2 mg, 353.97 umol, 69.83% yield, 98.226% purity) was obtained as white solid. LCMS (ESI) m/z 306.1 $[M+H]^+$

Synthesis of N-(4,4-dimethylcyclohexyl)-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



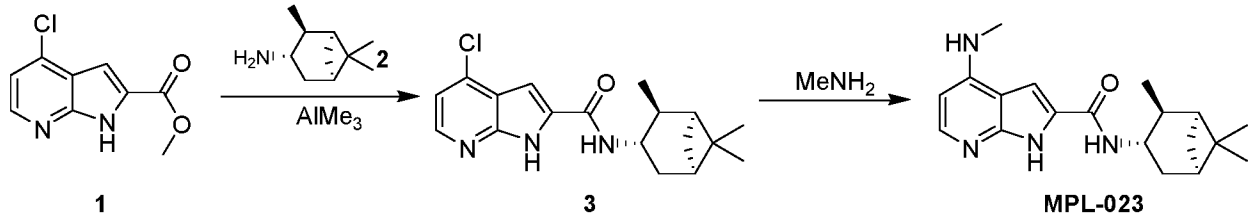
5 **MPL-018**

To a solution of 4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (100 mg, 327.01 umol, 1 *eq*) in methanamine (33.85 mg, 327.01 umol, 5 mL, 1 *eq*), the mixture was stirred at 120 °C for 24 hrs in a 30 mL of autoclave. TLC and LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 25:1) and prep. HPLC(column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 14%-34%,11min). The product N-(4,4-dimethylcyclohexyl)-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (42.1 mg, 118.74 umol, 36.31% yield, 97.702% purity, FA) was obtained as white solid.

LCMS (ESI) m/z 301.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 7.99 (br d, J = 7.1 Hz, 1H), 7.91 (d, J = 5.7 Hz, 1H), 7.19 - 7.16 (m, 1H), 7.11 (br s, 1H), 6.14 (br d, J = 5.5 Hz, 1H), 3.77 - 3.64 (m, 1H), 2.89 (br d, J = 4.6 Hz, 3H), 1.74 - 1.63 (m, 2H), 1.54 - 1.38 (m, 4H), 1.32 - 1.21 (m, 2H), 0.93 (d, J = 7.3 Hz, 6H).

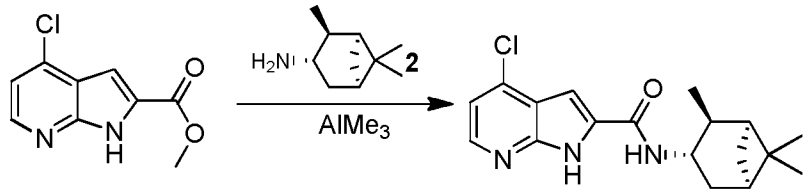
Example 46. MPL-023

Scheme



1 3 MPL-023

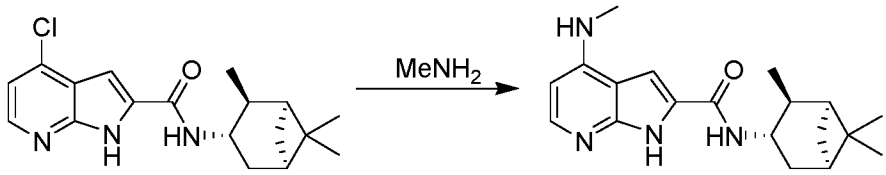
Synthesis of 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



1 3

To a solution of methyl 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (150 mg, 712.19 umol, 1 *eq*) in DCE (5 mL) was added (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (327.46 mg, 2.14 mmol, 3 *eq*) and trimethylalumane (2 M, 712.19 uL, 2 *eq*). The mixture was stirred at 50 °C for 36 hrs. TLC and LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was diluted with water (30 mL) and extracted with DCM: MeOH (30 mL **x** 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 200:1). The product 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (149 mg, 359.21 umol, 50.44% yield, 80% purity) was obtained as white solid.

Synthesis of 4-(methylamino)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H - pyrrolo[2,3-b]pyridine-2-carboxamide



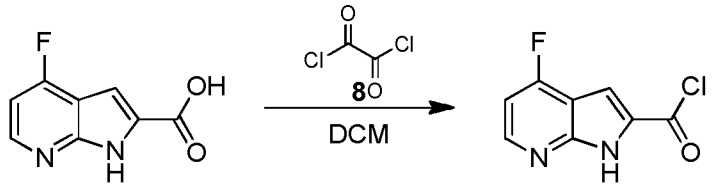
3 MPL-023

To a solution of 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine -2-carboxamide (100 mg, 301.35 umol, 1 *eq*) in methanamine (31.20 mg, 301.35 umol, 5 mL, 1 *eq*), the mixture was stirred at 120 °C for 12 hr in a 30 mL of autoclave. TLC and LC-MS showed the starting material 3 was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 50:1) and prep. HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 17%-37%,11min). The product 4-(methylamino)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl] -1H-pyrrolo[2,3-b]pyridine-2-carboxamide (41.5 mg, 109.15 umol, 36.22% yield, 97.963% purity, FA) was obtained as white solid.

LCMS (ESI) m/z 327.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 8.17 (br d, J = 8.4 Hz, 1H), 7.92 (d, J = 5.7 Hz, 1H), 7.33 - 7.25 (m, 1H), 7.22 (s, 1H), 6.18 (d, J = 5.7 Hz, 1H), 4.37 - 4.29 (m, 1H), 2.91 (d, J = 4.6 Hz, 3H), 2.46 - 2.36 (m, 2H), 2.08 - 2.00 (m, 1H), 1.94 (br s, 1H), 1.82 (br t, J = 5.3 Hz, 1H), 1.70 - 1.62 (m, 1H), 1.23 (s, 3H), 1.17 - 1.12 (m, 1H), 1.06 (t, J = 3.6 Hz, 6H).

Example 47. MPL-027

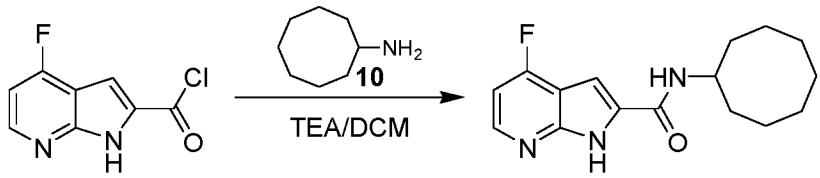
Synthesis of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DCM (5 mL) was added oxalyl dichloride (1.41 g, 11.10 mmol, 971.88 uL, 20 *eq*) and DMF (1.22 mg, 16.65 umol, 1.28 uL, 0.03 *eq*) under N_2, the mixture was stirred for 1.5 hr at 25 °C under N_2. TLC showed the starting material 7 was consumed completely and one main spot was detected. The mixture was concentrated under reduced pressure to give a residue. After concentration, the crude product as a yellow solid was used directly for the next step without

purification. The product 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (110.24 mg, 555.14 umol, 100.00% yield) as yellow solid was obtained.

Synthesis of N-cyclooctyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



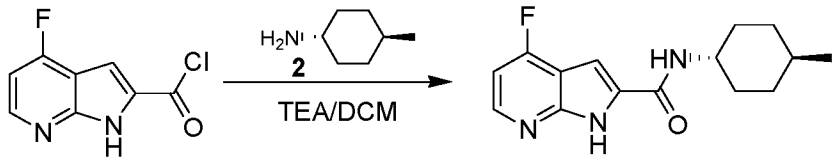
9 **MPL-027**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (110 mg, 553.93 umol, 1 *eq*) in DCM (3 mL) was added cyclooctanamine (105.71 mg, 830.89 umol, 1.5 *eq*) and TEA (112.10 mg, 1.11 mmol, 154.20 uL, 2 *eq*) under N_2 , the mixture was stirred at 25 °C for 12 hrs under N_2. TLC and LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with DCM (20 mL) and washed with HCl (1 M, 20 mL) and then extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 10:1). The product N-cyclooctyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (18.5 mg, 62.33 umol, 11.25% yield, 97.488% purity) was obtained as white solid.

LCMS (ESI) m/z 290.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ =12.44 (br s, 1H), 8.32 (dt, *J* = 3.0, 5.3 Hz, 2H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 5.4, 10.3 Hz, 1H), 4.10 - 3.96 (m, 1H), 1.81 - 1.67 (m, 6H), 1.59 - 1.46 (m, 8H).

Example 48. MPL-028

Synthesis of 4-fluoro-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



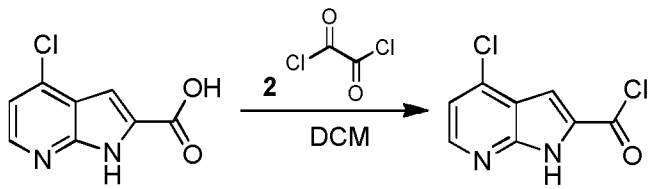
1 **MPL-028**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (110 mg, 553.93 umol, 1 *eq*) in DCM (3 mL) was added 4-methylcyclohexanamine (94.06 mg, 830.90 umol, 1.5 *eq*) and TEA (112.10 mg, 1.11 mmol, 154.20 uL, 2 *eq*) under N_2, the mixture was stirred at 25 °C for 3 hrs under N_2. TLC and LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with DCM (20 mL) and washed with HCl (1 M, 20 mL) and then extracted with DCM (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 10:1). The product 1 4-fluoro-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (24.3 mg, 84.80 umol, 15.31% yield, 96.08% purity) was obtained as white solid.

LCMS (ESI) m/z 275.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.45 (br s, 1H), 8.35 - 8.27 (m, 2H), 7.23 (s, 1H), 7.00 (dd, *J* = 5.4, 10.3 Hz, 1H), 3.79 - 3.66 (m, 1H), 1.86 (br d, *J* = 9.7 Hz, 2H), 1.71 (br d, *J* = 12.3 Hz, 2H), 1.41 - 1.28 (m, 3H), 1.10 - 0.97 (m, 2H), 0.89 (d, *J* = 6.4 Hz, 3H).

Example 49. MPL-033

Synthesis of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride

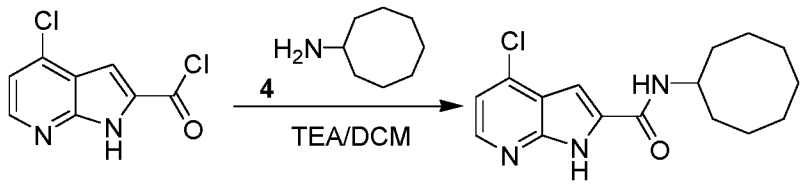


1 3

To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100.00 mg, 508.67 umol, 1 *eq*) in DCM (5 mL) was added oxalyl dichloride (645.64 mg, 5.09 mmol, 445.27 uL, 10 *eq*) and DMF (1.12 mg, 15.26 umol, 1.17 uL, 0.03 *eq*) under N_2, the mixture was stirred at 80 °C for 1.5 hrs. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The crude product 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (109 mg,

506.89 umol, 99.65% yield) was obtained as yellow solid and used directly for the next step without purification.

Synthesis of 4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



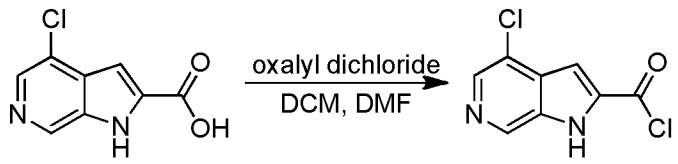
3 **MPL-033**

To a solution of 4-chloro-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (109 mg, 506.89 umol, 1 *eq*) and cyclooctanamine (128.98 mg, 1.01 mmol, 2 *eq*) in DCM (3 mL) was added TEA (102.58 mg, 1.01 mmol, 141.11 uL, 2 *eq*), the mixture was stirred at 25 °C for 0.5 hr under N_2. TLC and LC-MS showed the starting material 3 was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with solvent of DCM:MeOH = 10:1 (40 mL) and washed with brine (20 mL x2), then the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM:MeOH = 1:0 to 100:1). The product 4-chloro-N-cyclooctyl -1H-pyrrolo[2,3-b]pyridine-2-carboxamide (71.8 mg, 233.43 umol, 46.05% yield, 99.419% purity) was obtained as white solid.

LCMS (ESI) m/z 306.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.47 (s, 1H), 8.41 (d, *J* = 7.8 Hz, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 7.30 - 7.24 (m, 2H), 4.04 (br dd, *J* = 4.3, 8.5 Hz, 1H), 1.81 - 1.66 (m, 6H), 1.61 - 1.47 (m, 8H).

Example 50. MPL-034

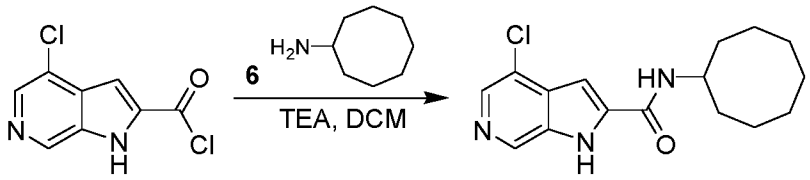
Synthesis of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carbonyl chloride



4 **5**

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 508.67 umol, 1 *eq*) in DCM (5 mL) was added oxalyl dichloride (645.64 mg, 5.09 mmol, 445.27 uL, 10 *eq*) and DMF (1.12 mg, 15.26 umol, 1.17 uL, 0.03 *eq*) under N_2, The mixture was stirred at 80 °C for 0.5 hr. LC-MS showed the starting material 4 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The crude product 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carbonyl chloride (109 mg, 506.89 umol, 99.65% yield) was obtained as yellow solid and used directly for the next step without purification. LCMS (ESI) m/z 211.0 $[M-Cl+OMe]^+$

Synthesis of 4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



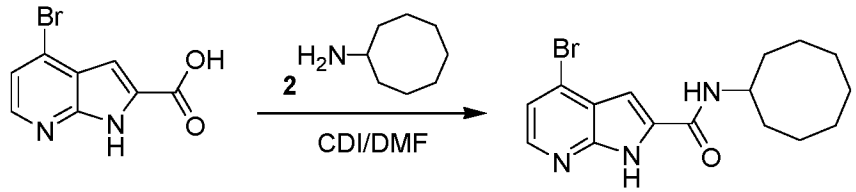
5 **MPL-034**

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carbonyl chloride (109 mg, 506.89 umol, 1 *eq*) in DCM (3 mL) was added cyclooctanamine (193.47 mg, 1.52 mmol, 3 *eq*) and TEA (153.88 mg, 1.52 mmol, 211.66 uL, 3 *eq*), the mixture was stirred at 25 °C for 0.5 hr under N_2. TLC and LC-MS showed the starting material **5** was consumed completely and one main peak with desired mass was detected. The reaction mixture was diluted with solvent of DCM:MeOH=10:1(40 mL) and washed with brine (20 mL x 2). Then the organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH =1:0 to 50:1). The product 4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (44.7 mg, 145.39 umol, 28.68% yield, 99.462% purity) was obtained as yellow solid. The product was confirmed by ^1H NMR. Purity comes from LCMS.

LCMS (ESI) m/z 306.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6)= 12.43 (br s, 1H), 8.72 (s, 1H), 8.62 (br d, *J*=7.9 Hz, 1H), 8.18 (s, 1H), 7.37 (s, 1H), 4.11 - 4.02 (m, 1H), 1.83 - 1.66 (m, 6H), 1.63 - 1.43 (m, 8H).

Example 51. MPL-035

Synthesis of 4-bromo-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



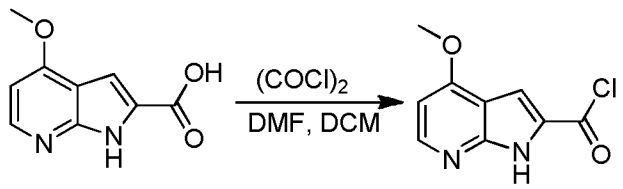
1 MPL-035

To a solution of 4-bromo-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 414.87 umol, 1 *eq*) and CDI (100.91 mg, 622.30 umol, 1.5 *eq*) in DMF (3 mL) the mixture was stirred at 25 °C for 30 min, then cyclooctanamine (79.17 mg, 622.30 umol, 1.5 *eq*) was added, the mixture was stirred at 25 °C for 12 h under N_2. TLC and LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was diluted with DCM (20 mL) and washed with water (20 mL x 5) and HCl (1 M, 20mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 200:1). The product 4-bromo-N-cyclooctyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide (74.4 mg, 209.36 umol, 50.47% yield, 98.562% purity) was obtained as white solid.

LCMS (ESI) m/z 350.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.47 (br s, 1H), 8.43 (br d, J = 7.5 Hz, 1H), 8.18 (br d, J = 4.9 Hz, 1H), 7.40 (br d, J = 4.6 Hz, 1H), 7.21 (br s, 1H), 4.04 (br s, 1H), 1.81 - 1.66 (m, 6H), 1.52 (br d, J = 9.9 Hz, 8H).

Example 52. MPL-038

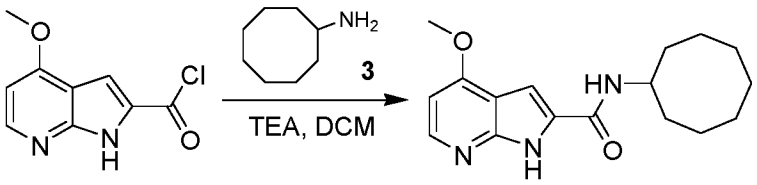
Synthesis of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride



1 2

To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 1.04 mmol, 1 *eq*) in DCM (4 mL) was added DMF (3.80 mg, 52.04 umol, 4.00 uL, 0.05 *eq*) and $(COCl)_2$ (2.90 g, 22.85 mmol, 2 mL, 21.95 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed the starting material 1 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was directly used in next step without any purification. Compound 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (200 mg, 902.11 umol, 86.68% yield, 95% purity) was obtained as a white solid. LCMS (ESI) m/z 206.9 $[M+H]^+$

Synthesis of N-cyclooctyl-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

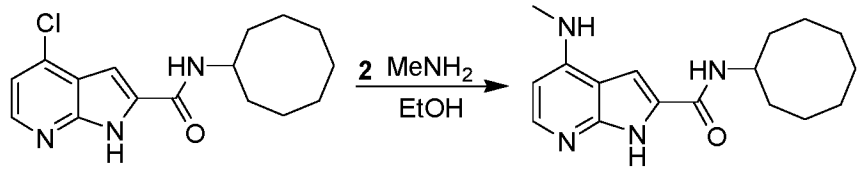


2 **MPL-038**

To a solution of 4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carbonyl chloride (200 mg, 949.59 umol, 1 *eq*) in DCM (6 mL) was added TEA (288.27 mg, 2.85 mmol, 396.52 uL, 3 *eq*) and cyclooctanamine (241.63 mg, 1.90 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 hrs. LCMS showed the starting material 2 was consumed and desire product formed. The mixture was directly concentrated under reduce pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 100 : 1 to 20 **:** 1). Compound N-cyclooctyl-4-methoxy -1H-pyrrolo[2,3-b]pyridine- 2-carboxamide (150 mg, 495.72 umol, 52.20% yield, 99.6% purity) was obtained as a white solid. LCMS (ESI) m/z 302.2 $[M+H]^+$

Example 53. MPL-040

N-cyclooctyl-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



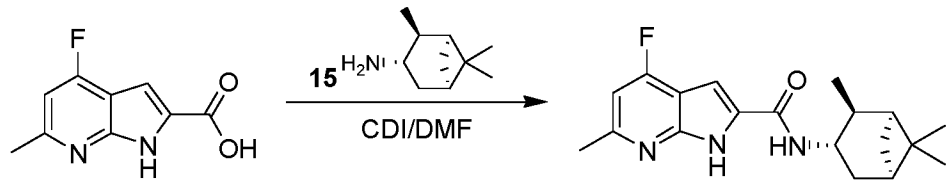
1 MPL-040

4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (100 mg, 327.01 umol, 1 *eq*) in methanamine (33.85 mg, 327.01 umol, 4 mL, 1 *eq*), the mixture was stirred at 120 °C for 12 hrs in a 30 mL of autoclave. TLC and LC-MS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM : MeOH = 1:0 to 30:1). The product N-cyclooctyl-4-(methylamino)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (41.9 mg, 135.75 umol, 41.51% yield, 97.323% purity) was obtained as white solid.

LCMS (ESI) m/z 239.0 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ = 11.51 (br s, 1H), 7.95 - 7.86 (m, 2H), 7.13 (s, 1H), 6.85 (br d, *J* = 4.8 Hz, 1H), 6.07 (d, *J* = 5.7 Hz, 1H), 4.01 (br s, 1H), 2.84 (br d, *J* = 4.4 Hz, 3H), 1.84 - 1.58 (m, 8H), 1.58 - 1.48 (m, 6H).

Example 54. MPL-043

Synthesis of 4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



14 MPL-043

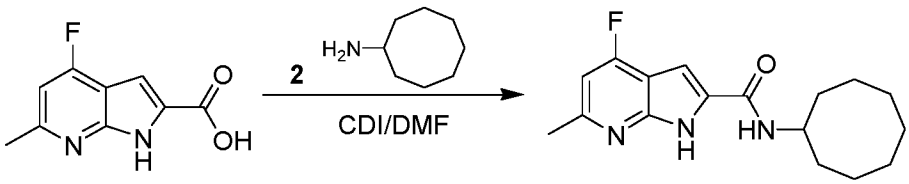
4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (650 mg, 502.16 umol, 1 *eq*) and CDI (122.14 mg, 753.24 umol, 1.5 *eq*) was added in DMF (4 mL), the mixture was stirred at 30 °C for 0.5h, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (76.96 mg, 502.16 umol, 1 *eq*) was added under N_2, the mixture was stirred at 30 °C for 0.5 h. LC-MS showed the starting

material 14 was consumed completely and one main peak with desired mass was detected. The mixture was added in water (20mL) and stirred for 10 mins, then filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give product. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 44%-74%,11min). The product 4-fluoro-6-methyl-N- [(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (10.1 mg, 30.41 umol, 6.06% yield, 99.184% purity) was obtained as white solid.

LCMS (ESI) m/z 330.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.25 (br s, 1H), 8.36 (br d, J = 8.3 Hz, 1H), 7.22 (s, 1H), 6.90 (d, J = 11.4 Hz, 1H), 4.40 - 4.30 (m, 1H), 2.53 (s, 3H), 2.45 - 2.35 (m, 2H), 2.06 (br t, J = 6.8 Hz, 1H), 1.94 (br s, 1H), 1.84 - 1.79 (m, 1H), 1.69 (br dd, J = 5.9, 12.9 Hz, 1H), 1.23 (s, 3H), 1.18 (br d, J = 9.6 Hz, 1H), 1.07 - 1.04 (m, 6H).

Example 55. MPL-044

Synthesis of N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



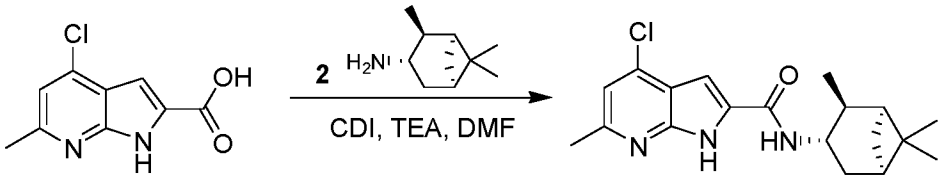
1 MPL-044

4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (500 mg, 386.27 umol, 1 *eq*) and CDI (93.95 mg, 579.41 umol, 1.5 *eq*) was added in DMF (3 mL), the mixture was stirred at 30 °C for 0.5h, then cyclooctanamine (49.14 mg, 386.27 umol, 1 *eq*) was added under N_2, the mixture was stirred at 30 °C for 0.5 h. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was added in water (20mL) and stirred for 10 mins, then filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give product. The residue was purified by prep-HPLC (nomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.225%FA)-ACN];B%: 39%-68%,11min). The product N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide (10 mg, 32.93 umol, 8.53% yield, 99.902% purity) was obtained as white solid.

LCMS (ESI) m/z 304.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 12.21 (br s, 1H), 8.23 (br d, J = 7.8 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 6.89 (d, J = 11.2 Hz, 1H), 4.09 - 3.96 (m, 1H), 2.53 (s, 3H), 1.82 - 1.66 (m, 6H), 1.60 - 1.44 (m, 8H).

Example 56. MPL-045

Synthesis of 4-chloro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



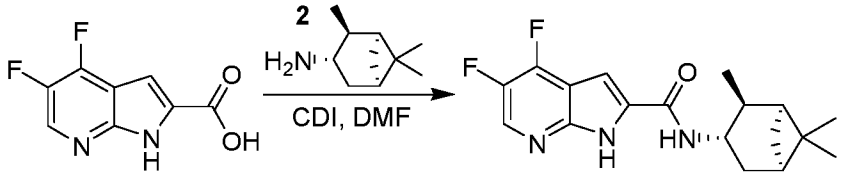
1 MPL-045

To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 949.59 umol, 1 *eq*) in DMF (5 mL) was added (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (291.08 mg, 1.90 mmol, 2 *eq*) and CDI (184.77 mg, 1.14 mmol, 1.2 *eq*). The mixture was stirred at 30 °C for 12 hrs. LCMS showed it was consumed completely and main desired compound. The mixture was diluted with EtOAc (30 mL). It was washed with aqueous 5% LiCl (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The filtrate residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1:1). Then the residue was lyophilized. Compound 4-chloro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide (200 mg, 558.08 umol, 58.77% yield, 96.51% purity) was obtained as a white solid.

LCMS (ESI) m/z 346.1 $[M+H]^+$; 1H NMR (400MHz, $CDCl_3$) 9.67 (br s, 1H), 7.06 (s, 1H), 6.85 (s, 1H), 6.09 (br d, J=8.4 Hz, 1H), 4.56 - 4.47 (m, 1H), 2.76 - 2.68 (m, 1H), 2.63 (s, 3H), 2.52 - 2.46 (m, 1H), 2.04 - 1.99 (m, 1H), 1.97 - 1.88 (m, 2H), 1.71 - 1.67 (m, 1H), 1.27 (s, 3H), 1.19 (d, J=7.2 Hz, 3H), 1.10 (s, 3H), 0.95 (d, J=9.9 Hz, 1H).

Example 57. MPL-062

4,5-difluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



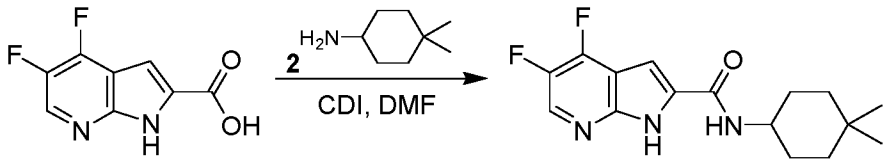
1 **MPL-062**

To a solution of 4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 504.73 umol, 1 *eq*) in DMF (1 mL) was added CDI (98.21 mg, 605.68 umol, 1.2 *eq*). The mixture was stirred at 25°C for 0.5h. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (92.83 mg, 605.68 umol, 1.2 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. LCMS showed desired compound mass was detected. TLC showed most of starting material was consumed and new spots were observed. The reaction mixture was added to water (15 mL). Then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 4,5-difluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (24.4 mg, 70.56 umol, 13.98% yield, 96.4% purity) was obtained as white solid.

LCMS (ESI) m/z 334.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.61 (br s, 1H), 8.50 - 8.47 (m, 1H), 7.34 (s, 1H), 4.42 - 4.30 (m, 1H), 2.45 - 2.41 (m, 1H), 2.37 (br s, 1H), 2.11 - 2.03 (m, 1H), 1.95 (br s, 1H), 1.82 (br s, 1H), 1.70 (br dd, J=5.3, 12.9 Hz, 1H), 1.23 (s, 3H), 1.18 (br d, J=9.3 Hz, 1H), 1.06 (br s, 6H).

Example 58. MPL-063

Synthesis of N-(4,4-dimethylcyclohexyl)-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carbox amide



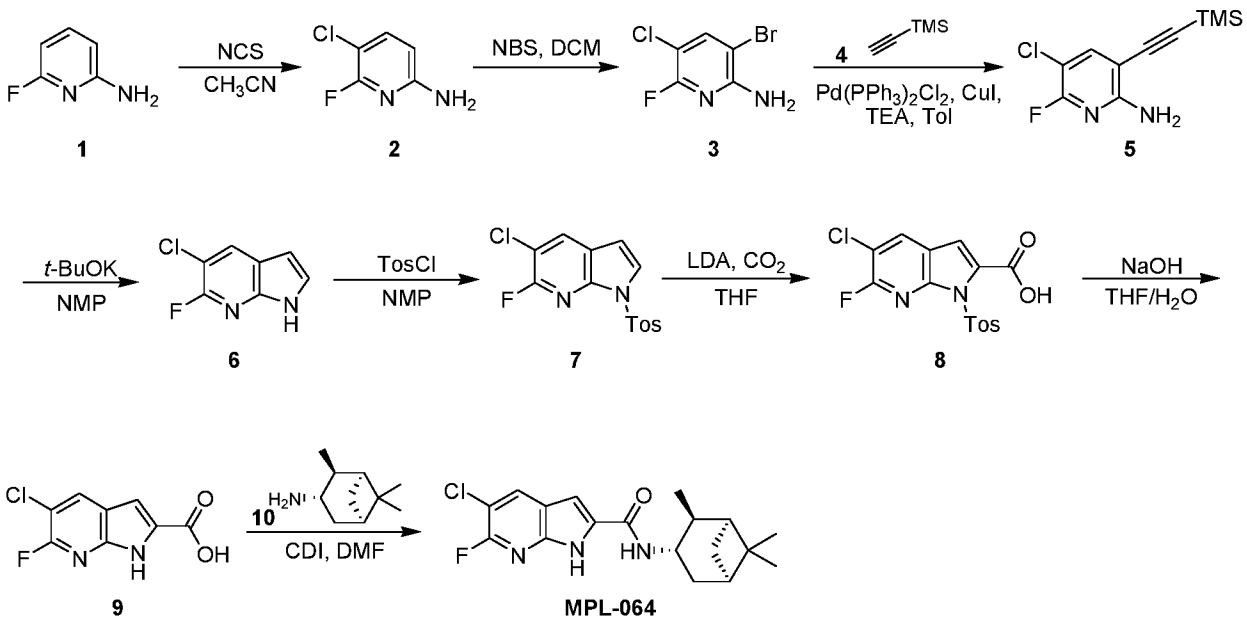
1 MPL-063

To a solution of 4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 504.73 umol, 1 *eq*) in DMF (1 mL) was added CDI (98.21 mg, 605.67 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 h. 4,4-dimethylcyclohexanamine (77.06 mg, 605.67 umol, 1.2 *eq*) was added and the mixture was stirred at 30 °C for 11.5 h. LCMS showed 27% of the starting material was still remained. The reaction mixture was added to water (15ml), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give crude product. The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 55%-75%,11min). The product N-(4,4-dimethylcyclohexyl) -4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (21.2 mg, 68.98 umol, 13.67% yield, 100% purity) was obtained as white solid. Purity comes from LCMS and the product was confirmed by ^{1}H NMR.

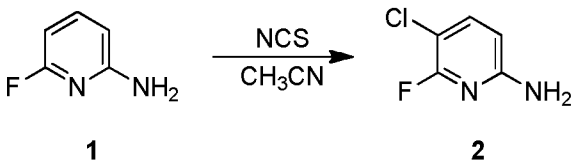
LCMS (ESI) m/z 308.1 $[M+H]^{+}$; ^{1}H NMR (400MHz, DMSO-d6) δ = 12.59 (br s, 1H), 8.52 - 8.46 (m, 1H), 8.36 (br d, J=7.8 Hz, 1H), 7.29 (s, 1H), 3.73 (br d, J=7.6 Hz, 1H), 1.68 (br d, J=9.8 Hz, 2H), 1.59 - 1.47 (m, 2H), 1.45 - 1.37 (m, 2H), 1.33 - 1.23 (m, 2H), 0.94 (d, J=8.1 Hz, 6H).

Example 59. MPL-064

Scheme

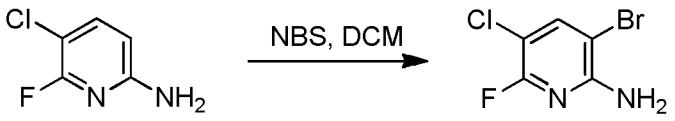


Synthesis of 3-bromo-5-chloro-6-fluoro-pyridin-2-amine



To a solution of NCS (28.59 g, 214.09 mmol, 1.2 *eq*) in CH_3CN (200 mL) was added 6-fluoropyridin-2-amine (20 g, 178.40 mmol, 1 *eq*), the mixture was stirred at 70 °C for 6 hrs. Then NCS (2 g) was added, the mixture was stirred at 70 °C for 4 h. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue and diluted with water (100mL), and extracted with EtOAc (150 mL **x** 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 1:0 to 10:1). The product 5-chloro-6-fluoro-pyridin-2-amine (16.7 g, 102.56 mmol, 57.49% yield, 90% purity) was obtained as brown solid.

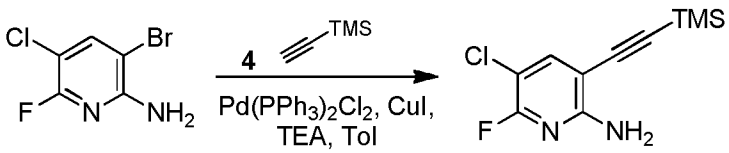
Synthesis of 3-bromo-5-chloro-6-fluoro-pyridin-2-amine



2 3

To a solution of 5-chloro-6-fluoro-pyridin-2-amine (16.7 g, 113.95 mmol, 1 *eq*) in DCM (200 mL) was added NBS (30.42 g, 170.93 mmol, 1.5 *eq*), the mixture was stirred at 25 °C for 1 hr. TLC showed the starting material 2 was consumed completely and one main spot was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The product 3-bromo-5-chloro-6-fluoro-pyridin-2-amine (21.0 g, 88.49 mmol, 77.65% yield, 95% purity) was obtained as brown solid.

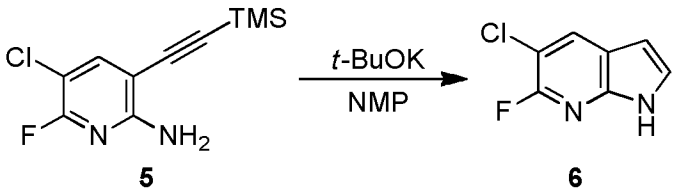
Synthesis of 5-chloro-6-fluoro-3-(2-trimethylsilylethynyl)pyridin-2-amine



3 5

To a solution of 3-bromo-5-chloro-6-fluoro-pyridin-2-amine (10 g, 44.36 mmol, 1 *eq*) in TEA (80 mL) was added ethynyl(trimethyl)silane (43.57 g, 443.57 mmol, 61.45 mL, 10 *eq*) CuI (2.53 g, 13.31 mmol, 0.3 *eq*) $Pd(PPh_3)_4$ (2.56 g, 2.22 mmol, 0.05 *eq*), the mixture was stirred at 50 °C for 12 hr under N_2. LC-MS showed the starting material 3 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 50:1). The product 5-chloro-6-fluoro-3-(2-trimethylsilylethynyl)pyridin-2-amine (9.2 g, 30.32 mmol, 68.35% yield, 80% purity) was obtained as brown solid. LCMS (ESI) m/z 243.1 $[M+H]^+$

Synthesis of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine

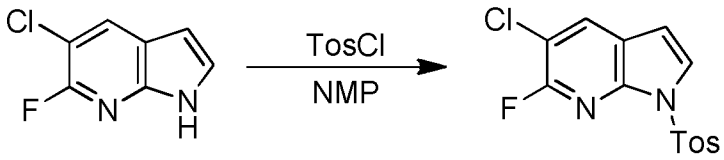


5 6

To a solution of 5-chloro-6-fluoro-3-(2-trimethylsilylethynyl)pyridin-2-amine (9.2 g, 37.90 mmol, 1 *eq*) in NMP (100 mL) was added KOtBu (12.76 g, 113.70 mmol, 3 *eq*) under N_2. The mixture was stirred at 80 °C for 12 hrs. LCMS showed starting material 5 was consumed completely. The mixture as crude product was used directly for the next step.

LCMS (ESI) m/z 171.0 $[M+H]^+$

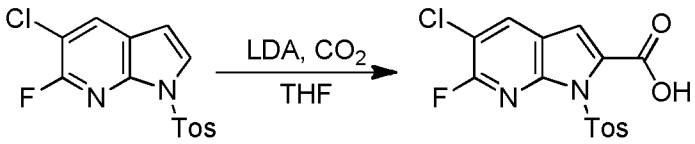
Synthesis of 5-chloro-6-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



6 7

To a solution of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine (6.46 g, 37.87 mmol, 1 *eq*) in NMP (80 mL) was added TosCl (14.44 g, 75.75 mmol, 2 *eq*) under N_2. The mixture was stirred at 25 °C for 12 hr. LCMS showed starting material 6 was consumed completely and one main peak with desired mass was detected. The reaction mixture was added to water (500 mL) and extracted with (200mL x 4). The organic layers were dried over **anhydrous Na_2SO_4** and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 1/0 to 10/1). The product 5-chloro-6-fluoro-1-(p-tolylsulfonyl) pyrrolo[2,3-b]pyridine (2.4 g, 7.02 mmol, 18.54% yield, 95% purity) was obtained as white solid.

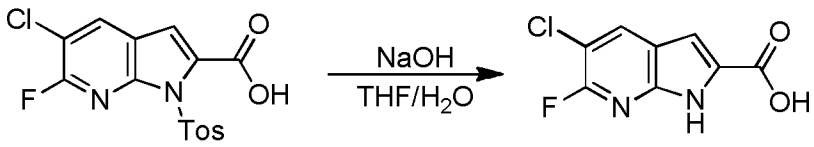
Synthesis of 5-chloro-6-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid



7 8

LDA (2 M, 4.06 mL, 1.1 *eq*) was added to a solution of 5-chloro-6-fluoro-1-(p-tolylsulfonyl) pyrrolo[2,3-b]pyridine (2.4 g, 7.39 mmol, 1 *eq*) in THF (50 mL) at -70 °C under N_2, then the mixture was stirred for 1 h, then CO_2 (325.24 mg, 7.39 mmol, 1 *eq*) was added, the mixture was stirred at -70 °C for 0.5 h. LC-MS showed desired product was detected. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (30 mL) at -70 °C, and then concentrated under reduced pressure to remove THF and then diluted with 50 mL water, filtered and the filter cake was washed with 50 mL of water, dried under reduced pressure to give the crude product. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 1:0 to 1:1 contained 1% AcOH). The product 5-chloro-6-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2- carboxylic acid (800 mg, 2.06 mmol, 27.89% yield, 95% purity) was obtained as yellow solid.

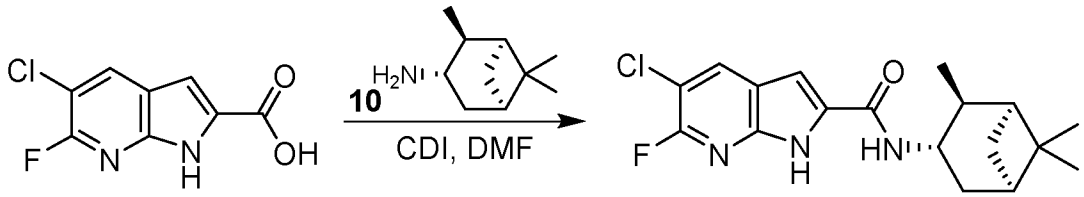
Synthesis of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



8 9

To a solution of 5-chloro-6-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (750 mg, 2.03 mmol, 1 *eq*) and NaOH (2 M, 4.29 mL, 4.22 *eq*) in THF (4 mL), the mixture was stirred at 75 °C for 3 hr. LC-MS showed the starting material 8 was consumed completely. The mixture was concentrated under reduced pressure to remove the THF, then acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 10 mL x 3 of Petroleum ether, dried under reduced pressure to give the product. The product 5-chloro-6-fluoro-1H-pyrrolo[2,3-b] pyridine-2-carboxylic acid (350 mg, 1.55 mmol, 76.19% yield, 95% purity) was obtained as white solid.

Synthesis of 5-chloro-6-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



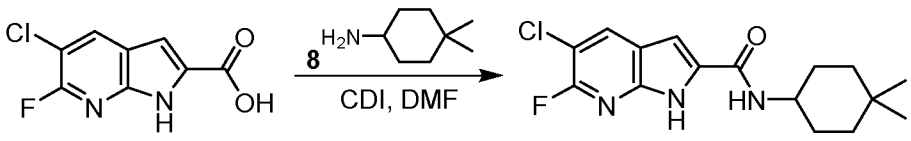
9 **MPL-064**

To a solution of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (175 mg, 815.54 umol, 1 *eq*) and CDI (198.36 mg, 1.22 mmol, 1.5 *eq*) in DMF (2 mL) the mixture was stirred at 25 °C for 30 min, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (187.49 mg, 1.22 mmol, 1.5 *eq*) was added, the mixture was stirred at 25 °C for 0.5 h under N_2. LC-MS showed one main peak with desired mass was detected. The mixture was added to a solution of LiCl (100ml, 3%), filtered and the filter cake was washed with 20 mL of water, dried under reduced pressure to give residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 1/0 to 10/1). The product 5-chloro-6-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide (126.3 mg, 359.79 umol, 44.12% yield, 99.655% purity) was obtained as white solid.

LCMS (ESI) m/z 350.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) δ = 9.82 (br s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.05 (br d, *J* = 8.3 Hz, 1H), 4.55 (br s, 1H), 2.79 - 2.70 (m, 1H), 2.53 - 2.45 (m, 1H), 2.03 (br d, *J* = 2.6 Hz, 1H), 1.96 - 1.88 (m, 2H), 1.68 (br dd, *J* = 2.2, 6.1 Hz, 1H), 1.27 (s, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.12 (s, 3H), 0.93 (d, *J* = 9.6 Hz, 1H).

Example 60. MPL-065

Synthesis of 5-chloro-N-(4,4-dimethylcyclohexyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine e-2-carboxamide



7 **MPL-065**

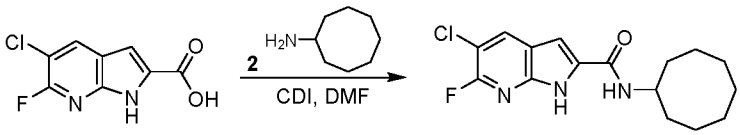
To a solution of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 932.05 umol, 1 *eq*) in DMF (2 mL) was added CDI (226.70 mg, 1.40 mmol, 1.5 *eq*), the mixture was

stirred at 30°Cfor 0.5h, then 4,4-dimethylcyclohexanamine (177.87 mg, 1.40 mmol, 1.5 *eq*) was added and the mixture was stirred at 30°C for another 0.5h. TLC and LC-MS showed the starting material 7 was consumed completely and one main peak with desired mass was detected. The mixture was added to water(20mL), and stirred for 10min, filtered and the filter cake was dried under reduced pressure to give the crude product. The crude product was purified by column chromatography (SiO2, DCM: MeOH = 1:0 to 500:1). The product 5-chloro-N-(4,4-dimethylcyclohexyl) -6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (89.2 mg, 271.55 umol, 29.13% yield, 98.572% purity) was obtained as white solid. Purity comes from LCMS. The product was confirmed by ^{1}H NMR.

LCMS (ESI) m/z 324.1 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-δ_6) = 12.48 (s, 1H), 8.49 (d, *J*=9.5 Hz, 1H), 8.34 (d, *J*=7.9 Hz, 1H), 7.18 (d, *J*=1.8 Hz, 1H), 3.77 - 3.67 (m, 2H), 1.71 - 1.63 (m, 2H), 1.52 (br d, *J*=14.6 Hz, 2H), 1.40 (br d, *J*=12.5 Hz, 2H), 1.31 - 1.23 (m, 2H), 0.93 (d, *J*=9.8 Hz, 6H).

Example 61. MPL-065A

Synthesis of 5-chloro-N-cyclooctyl-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



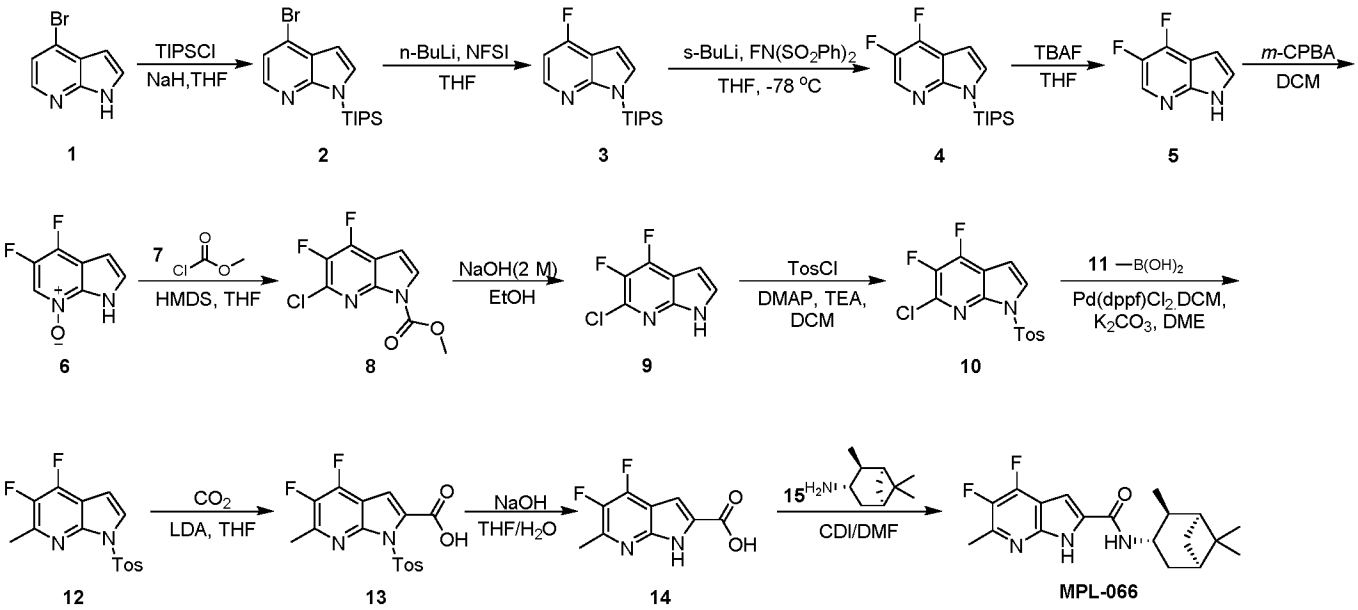
1 MPL-065A

To a solution of 5-chloro-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (175 mg, 815.54 umol, 1 *eq*) and CDI (198.36 mg, 1.22 mmol, 1.5 *eq*) in DMF (2 mL) the mixture was stirred at 25 °C for 30 min, then cyclooctanamine (155.64 mg, 1.22 mmol, 1.5 *eq*) was added. The mixture was stirred at 25 °C for 0.5 h under N_2. LC-MS showed one main peak with desired mass was detected. The mixture was added to a solution of LiCl (100ml, 3%), filtered and the filter cake was washed with 20 mL of water, dried under reduced pressure to give residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc = 1/0 to 10/1). The product 5-chloro-N-cyclooctyl-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (51.3 mg, 157.03 umol, 19.25% yield, 99.113% purity) was obtained as white solid.

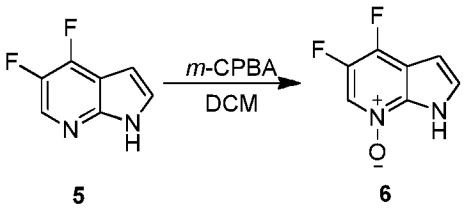
LCMS (ESI) m/z 324.1 $[M+H]^+$; ^1H NMR (400MHz, CHLOROFORM-d) δ = 9.57 (br s, 1H), 8.05 (d, *J* = 8.8 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.07 (br d, *J* = 8.3 Hz, 1H), 4.23 (br s, 1H), 2.00 - 1.93 (m, 2H), 1.78 - 1.61 (m, 12H), 1.77 - 1.54 (m, 1H).

Example 62. MPL-066

Scheme



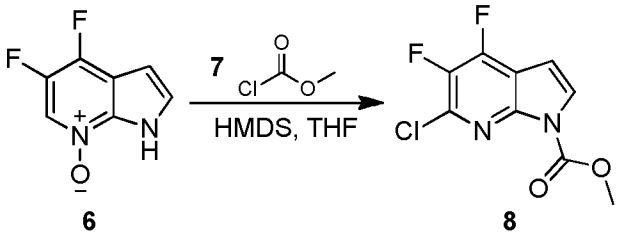
Synthesis of 4,5-difluoro-1H-pyrrolo[2,3-b]pyridine



To a solution of 4,5-difluoro-1H-pyrrolo[2,3-b]pyridine (3.2 g, 20.76 mmol, 1 *eq*) in DCM (30 mL) was dropwise added m-CPBA (17.92 g, 83.05 mmol, 80% purity, 4 *eq*) in THF (20 mL) at 0 °C. The mixture was stirred at 15 °C for 12 hr. LCMS showed it were main starting material. The mixture was quenched by the addition of the saturated Na_2SO_3 (5 mL), then dropwise added saturated Na_2CO_3. The mixture was extracted with Dichloromethane : Methanol (V:V=10:1), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by

column chromatography (SiO_2, Petroleum ether ： EtOAc = 5:2 to Dichloromethane : Methanol =10:1). Compound 4,5-difluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (3.35 g, 15.75 mmol, 75.87% yield, 80% purity) was obtained as a white solid.

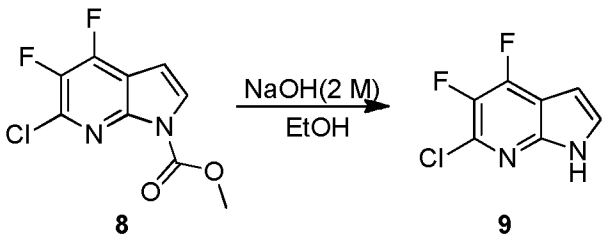
Synthesis of methyl 6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridine-1-carboxylate



6 8

To a solution of 4,5-difluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (2.8 g, 16.46 mmol, 1 *eq*) in THF (30 mL) was added HMDS (2.66 g, 16.46 mmol, 3.45 mL, 1 *eq*) and methyl carbonochloridate (4.67 g, 49.38 mmol, 3.82 mL, 3 *eq*) (9.55 g)at 0 °C. The mixture was stirred at 10 °C for 12 hr. LCMS showed there was no starting material. The mixture was concentrated in reduced pressure until without THF. The residue was added saturated $NaHCO_3$ (20 mL). The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with saturated brine (10 mL x 2), dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether ： EtOAc = 1:0 to 5:1). Compound methyl 6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridine-1-carboxylate (2.31 g, 6.56 mmol, 39.84% yield, 70% purity) was obtained white solid.

Synthesis of 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine

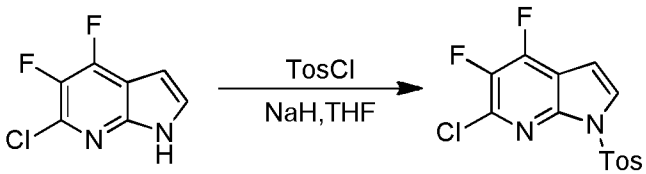


8 9

To a solution of methyl 6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridine-1-carboxylate (2.31 g, 9.37 mmol, 1 *eq*) in THF (11 mL) was added NaOH (2 M, 11 mL, 2.35 *eq*). The mixture was stirred

at 10 °C for 12 hr. LCMS showed there was no starting material. The mixture was concentrated in reduced pressure until without THF. The mixture was extracted with EtOAc (10 x 3 mL), the organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was used directly for next step without further purification. Compound 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine (1.460 g, 4.65 mmol, 49.59% yield, 60% purity) was obtained as a white solid.

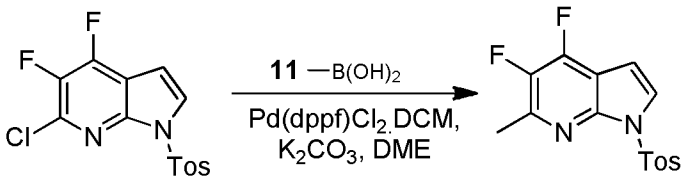
Synthesis of 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



9 **10**

To a solution of NaH (1.38 g, 34.47 mmol, 60% purity, 10 *eq*) in THF(10 mL) was added a solution of 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine (650 mg, 3.45 mmol, 1 *eq*) in THF(10 mL) at 0 °C under N_2, then 4-methylbenzenesulfonyl chloride (1.97 g, 10.34 mmol, 3 *eq*)was added at 0 °C under N_2. The mixture was stirred at 10 °C for 12 hrs under N_2 atmosphere. TLC (Petroleum ether : EtOAc = 5:1) showed there was no starting material. The reaction was quenched at -0°C with saturated aqueous NH_4Cl (5 mL). The aqueous phase was extracted with EtOAc (20 mL x 3). The combined hexane phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether ： EtOAc = 1:0 to 5:1). The product 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.1 g, 2.89 mmol, 83.79% yield, 90% purity) was obtained as a white solid.

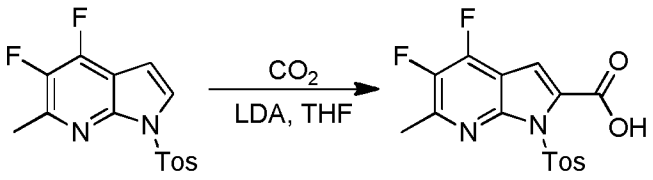
Synthesis of 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine



10 12

To a solution of 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.22 g, 3.56 mmol, 1 *eq*), methylboronic acid (1.07 g, 17.80 mmol, 5 *eq*), K_2CO_3 (1.48 g, 10.68 mmol, 3 *eq*) and Pd(dppf)Cl_2 DCM (260.45 mg, 355.95 umol, 0.1 *eq*) was added in DME (30 mL), the mixture was stirred at 110 °C for 12 hr under N_2. LCMS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: EtOAc = 1:0 to 1:1). The product 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (850.27 mg, 2.37 mmol, 66.70% yield, 90% purity) was obtained as white solid.

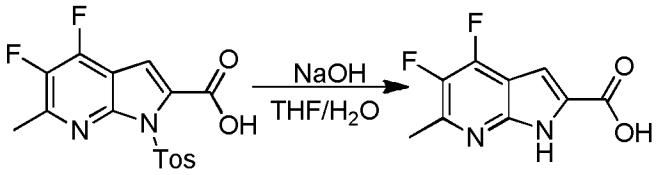
Synthesis of 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxalic acid



12 13

To a solution of 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (500 mg, 1.55 mmol, 1 *eq*) in THF(5 mL) at -78 °C under N_2 was treated dropwise with LDA (2 M, 1.16 mL, 1.5 *eq*). The reaction was stirred for 1.5h. The mixture was stirred for 10.5 h at 10 °C under CO2 (68.27 mg, 1.55 mmol, 1 *eq*). LCMS showed there was no starting material and main desired compound. The reaction was quenched at - 78°C with saturated aqueous NH_4Cl (5mL). The aqueous phase was extracted with EtOAc (5mL x 3). The combined hexane phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was used directly for next step without further purification. The product 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (427 mg, 699.35 umol, 45.08% yield, 60% purity) was obtained as white oil.

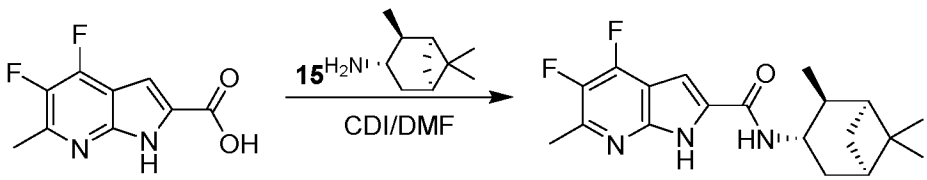
Synthesis of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



13 **14**

To a solution of 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 272.97 umol, 1 *eq*) in THF (1 mL) was dropwise added TBAF (1 M, 818.91 uL, 3 *eq*). The mixture was stirred at 80 °C for 12 hr. LCMS showed there was no starting material. The mixture was concentrated in reduced pressure until without THF. The residue was dissolved with EtOAc (20 mL). The organic phase was washed saturated brine (20 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was used directly for next step without further purification. Compound 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (26 mg, 91.91 umol, 33.67% yield, 75% purity) was obtained as a white solid.

Synthesis of 4,5-difluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



14 **MPL-066**

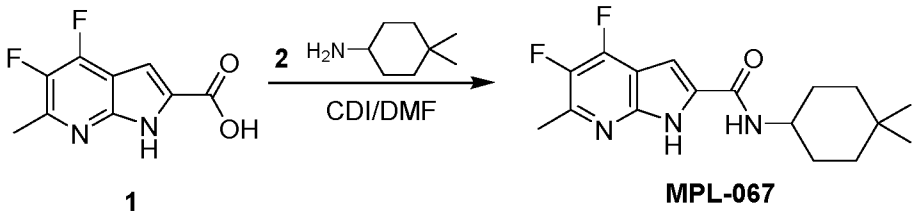
To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (46 mg, 216.82 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (38.67 mg, 238.51 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (34.89 mg, 227.67 umol, 1.05 *eq*) was added. The mixture was stirred at 30°C for 11.5 h. LCMS showed there was no starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transferred in bottom flask. The crude product was purified by prep-TLC (SiO_2, Petroleum ether : EtOAc =5:1). Compound 4,5-difluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-

pyrrolo[2,3-b]pyridine-2-carboxamide (6.4 mg, 18.42 umol, 8.50% yield, 100% purity) was obtained as a white solid.

LCMS (ESI), m/z 348.4[M+H]$^+$; 1H NMR (400MHz, CHLOROFORM-d) δ = 9.92 (br s, 1H), 6.86 (s, 1H), 6.12 (br d, *J*=7.4 Hz, 1H), 4.61 - 4.45 (m, 1H), 2.77 - 2.68 (m, 1H), 2.64 (br d, *J*=2.7Hz, 3H), 2.47 (br s, 1H), 2.05 - 1.88 (m, 3H), 1.81 - 1.62 (m, 2H), 1.26 (s, 3H), 1.19 (br d, *J*=7.0 Hz, 3H), 1.10 (s, 3H).

Example 63. MPL-067

Synthesis of 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]Pyridine -2-carboxamide



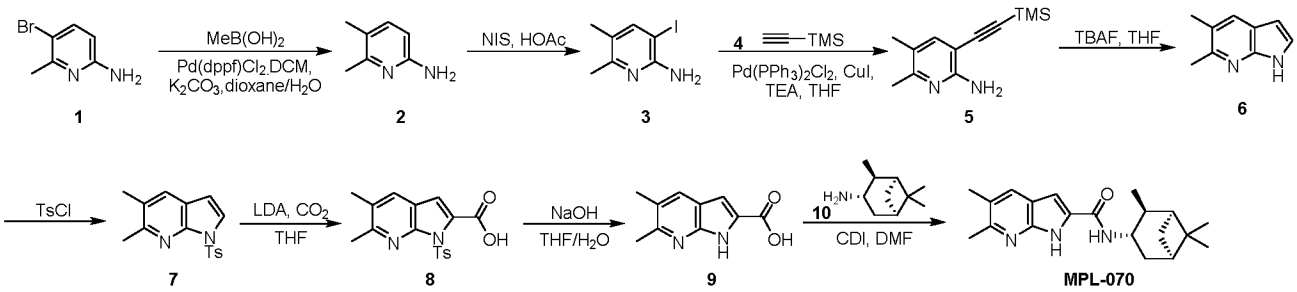
1 **MPL-067**

To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 *eq*) in DMF (1 mL) was added CDI (33.63 mg, 207.40 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 4,4-dimethylcyclohexanamine (26.39 mg, 207.40 umol, 1.1 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there was no starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transferred in bottom flask. The crude product was purified by prep-TLC (SiO_2, Petroleum ether : EtOAc =5:1). Compound N-(4,4-dimethylcyclohexyl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (8.4 mg, 25.96 umol, 13.77% yield, 99.326% purity) was obtained as a white solid.

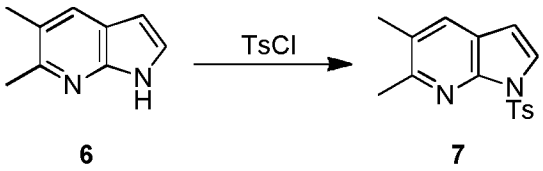
LCMS (ESI), m/z 322.[M+H]$^+$; ^{1}H NMR (400MHz, DMSO-d$_6$) δ = 12.39 (br s, 1H), 8.30 (d, *J*=7.8 Hz, 1H), 7.23 (s, 1H), 3.72 (br d, *J*=7.4 Hz, 1H), 2.54 - 2.52 (m, 3H), 1.67 (br d, *J*=9.4 Hz,2H), 1.58 - 1.46 (m, 2H), 1.45 - 1.37 (m, 2H), 1.29 (br d, *J*=12.5 Hz, 2H), 0.93 (d, *J*=8.2 Hz, 6H).

Example 64. MPL-070

Scheme

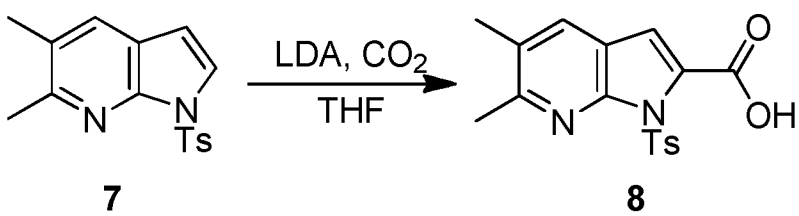


Synthesis of 5,6-dimethyl-1-tosyl-1H-pyrrolo[2,3-b]pyridine



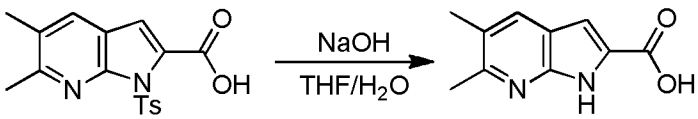
To a solution of 5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine (1.31 g, 8.96 mmol, 1 *eq*) in NMP (20 mL) was added 4-methylbenzenesulfonyl chloride (2.05 g, 10.75 mmol, 1.2 *eq*). The mixture was stirred at 20 °C for 3 hr. TLC indicated Reactant 6 was consumed completely and many new spots formed. The mixture was quenched with water (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/Petroleum ether gradient at 40 mL/min). Compound 5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.5 g, 4.99 mmol, 55.73% yield) was obtained as a white solid.

Synthesis of 5,6-dimethyl-1-tosyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



To a solution of 5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.5 g, 4.99 mmol, 1 *eq*) in THF (50 mL) was added dropwise LDA (2 M, 2.62 mL, 1.05 *eq*) at -78°C. After addition, the mixture was stirred at this temperature for 1hr under N_2 atmosphere, and then the resulting mixture was stirred at -78 °C for 2 hr under CO_2 atmosphere (15 psi). LC-MS showed Reactant 7 was consumed completely and one main peak with desired mass was detected. The mixture was quenched with NH_4Cl (100 mL) and extracted with EtOAc (100 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~5% MeOH/DCM at 40mL/min). Compound 5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine- 2-carboxylic acid (1.3 g, 3.77 mmol, 75.59% yield) was obtained as a white solid.

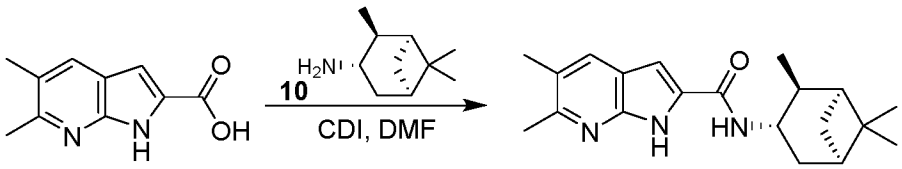
Synthesis of 5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



8 **9**

To a solution of 5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (1.1 g, 3.19 mmol, 1 *eq*) in EtOH (12 mL) was added NaOH (2 M, 12 mL, 7.51 *eq*), the resulting mixture was stirred at 80 °C for 12 hr. LC-MS showed Reactant 8 was consumed completely and one main peak with desired mass was detected. The mixture was acidified until the precipitate was formed and filtered. The filter cake was washed with MeCN (10 mL) and filtered; the filter cake was dried to give the product. The crude was used directly in the next step without further purification. The crude product 5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (0.52 g, 2.62 mmol, 82.17% yield, 96% purity) as a pale solid was used into the next step without further purification.

Synthesis of 5,6-dimethyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



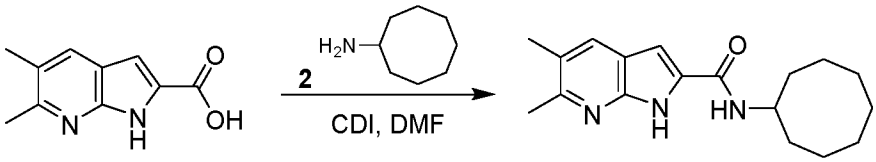
9 MPL-070

To a solution of 5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (0.15 g, 788.65 umol, 1 *eq*) in DMF (3 mL) was added CDI (191.82 mg, 1.18 mmol, 1.5 *eq*) and (1S,2S,3S,5R)- 2,6,6-trimethylnorpinan-3-amine (145.05 mg, 946.38 umol, 1.2 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed Reactant 9 was consumed completely and one main peak with desired mass was detected. The mixture was quenched with water (50 mL) and filtered. The filter cake was washed with MeOH (10 mL) and filtered. The filter cake was dried to give the product. Compound 5,6-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan- 3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (180 mg, 553.09 umol, 70.13% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 326.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ =11.73 (s, 1H), 8.25 (d, *J*=8.5 Hz, 1H), 7.77 (s, 1H), 7.04 (d, *J*=2.1 Hz, 1H), 4.44 - 4.29 (m, 1H), 2.48 (s, 3H), 2.44 (br d,*J*=2.1 Hz, 1H), 2.39 - 2.35 (m, 1H), 2.32 (s, 3H), 2.07 (br t, *J*=6.7 Hz, 1H), 1.95 (br d, *J*=2.7 Hz, 1H), 1.82 (br t, *J*=5.2 Hz, 1H), 1.73 - 1.63 (m, 1H), 1.24 (s,3H), 1.20 (d, *J*=9.5 Hz, 1H), 1.11 - 1.04 (m, 6H);

Example 65. MPL-071

Synthesis of N-cyclooctyl-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



1 MPL-071

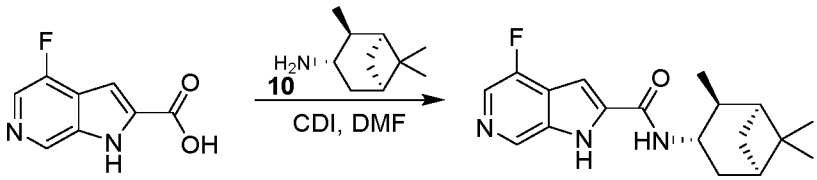
To a solution of 5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 525.77 umol, 1 *eq*) in DMF (1 mL) was added CDI (110.83 mg, 683.50 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. cyclooctanamine (86.96 mg, 683.50 umol, 1.3 *eq*) was added and the

reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by silica column chromatography (eluent of 20~80% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 1:1, Rf = 0.3) were combined and evaporated. Compound N-cyclooctyl-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (65 mg, 215.10 umol, 40.91% yield, 99.08% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 300.2 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ =11.71 (s, 1H), 8.12 (br d, *J*=7.9 Hz, 1H), 7.76 (s, 1H), 7.01 (d, *J*=1.7 Hz, 1H), 4.07 - 3.98 (m, 1H), 2.48 (s, 3H), 2.31 (s,3H), 1.82 - 1.65 (m, 6H), 1.63 - 1.45 (m, 8H).

Example 66. MPL-092

Synthesis of 4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide



10 **MPL-092**

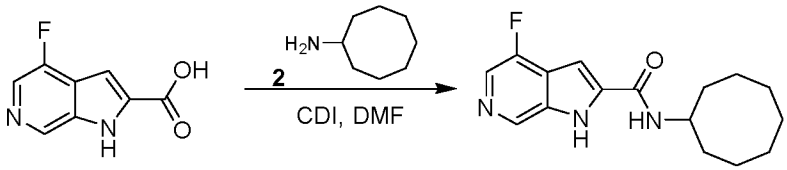
To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added CDI (117.02 mg, 721.68 umol, 1.3 *eq*). The mixture was stirred at 15 °C for 0.5 h. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (110.61 mg, 721.68 umol, 1.3 *eq*) was added. The mixture was stirred at 15 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. Then the crude product was purified by silica column chromatography (eluent of 20~70% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum ether: EtOAc = 1:1, R_f =

0.3) were combined and evaporated. Compound 4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl] -1H-pyrrolo[2,3-c]pyridine-2-carboxamide (30 mg, 94.36 umol, 17.00% yield, 99.20% purity) was obtained as a white solid.

LCMS (ESI) m/z 316.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ =12.47 (br s, 1H), 8.67 - 8.60 (m, 2H), 8.09 (s, 1H), 7.38 (s, 1H), 4.43 - 4.31 (m, 1H), 2.45 - 2.29 (m, 2H), 2.07 (br t, *J*=7.0Hz, 1H), 1.94 (br s, 1H), 1.80 (br s, 1H), 1.70 (br dd, *J*=5.5, 12.9 Hz, 1H), 1.23 - 1.17 (m, 4H), 1.07 - 1.03 (m, 6H).

Example 67. MPL-093

Synthesis of N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide

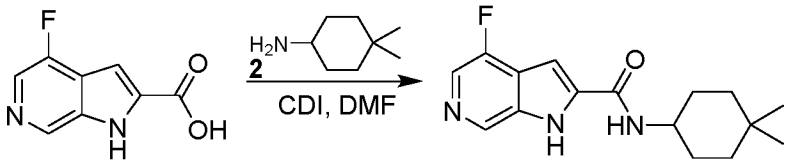


To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (2 mL) was added CDI (117.02 mg, 721.68 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then cyclooctanamine (91.82 mg, 721.68 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was delivered without further purification. Compound N-cyclooctyl-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (70 mg, 238.22 umol, 42.91% yield, 98.47% purity) was obtained as a white solid.

LCMS (ESI) m/z 290.1 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ =12.40 (br s, 1H), 8.62 (br s, 1H), 8.52 (br d, *J*=7.8 Hz, 1H), 8.05 (s, 1H), 7.34 (s, 1H), 7.38 - 7.28 (m, 1H), 7.38 - 7.28 (m, 1H), 7.38 - 7.28 (m, 1H), 7.38 - 7.28 (m, 1H), 7.38 - 7.28 (m, 1H), 4.03 (br s, 1H), 1.81 - 1.63 (m, 6H), 1.59 - 1.45 (m, 1H), 1.59 - 1.45 (m, 7H).

Example 68. MPL-094

N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

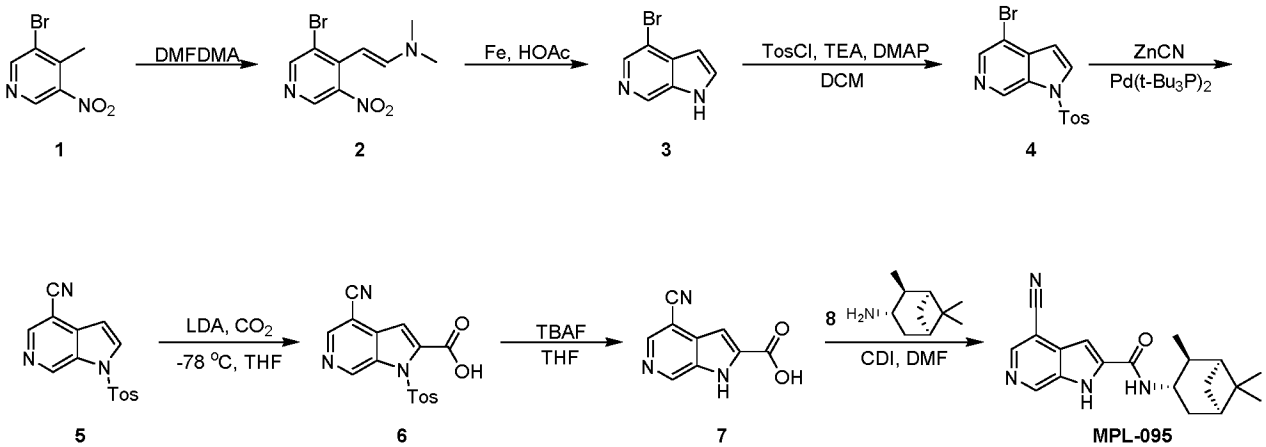


To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added CDI (108.02 mg, 666.16 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 h. 4,4-dimethylcyclohexanamine (84.75 mg, 666.16 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed desired compound mass was detected. The reaction mixture was added to water (15ml). Then it was filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give crude product. The product N-(4,4-dimethylcyclohexyl) -4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (36.5 mg, 119.84 umol, 21.59% yield, 95% purity) was obtained as white solid.

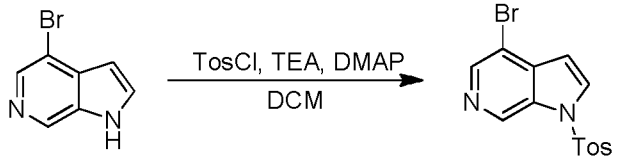
LCMS (ESI) m/z 290.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.44 (br s, 1H), 8.64 (d, *J*=2.2 Hz, 1H), 8.52 (br d, *J*=7.9 Hz, 1H), 8.08 (s, 1H), 7.33 (s, 1H), 3.75 (br s, 1H), 1.68 (br d, *J*=10.5 Hz, 2H), 1.61 - 1.48 (m, 2H), 1.45 - 1.37 (m, 2H), 1.30 (br d, *J*=12.3 Hz, 2H), 0.94 (d, *J*=8.8 Hz, 6H).

Example 69. MPL-095

Scheme



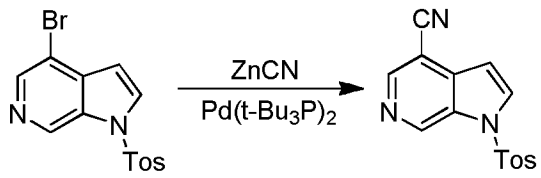
Synthesis of 4-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine



3 4

To a solution of 4-bromo-1H-pyrrolo[2,3-c]pyridine (3.11 g, 15.78 mmol, 1 *eq*) in DCM (50 mL) was added TosCl (3.91 g, 20.52 mmol, 1.3 *eq*), DMAP (192.83 mg, 1.58 mmol, 0.1 *eq*) and TEA (3.19 g, 31.57 mmol, 4.39 mL, 2 *eq*). The mixture was stirred at 15 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The mixture was concentrated in reduced pressure. The crude product was purified by silica column chromatography (eluent of 0~50% EtOAc/Petroleum ether gradient, 40 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc =3:1, Rf = 0.3) were combined and evaporated. Compound 4-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (5 g, 13.52 mmol, 85.68% yield, 95% purity) was obtained as a yellow solid. LCMS (ESI) m/z 352.4 $[M+H]^+$

Synthesis of 1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-4-carbonitrile

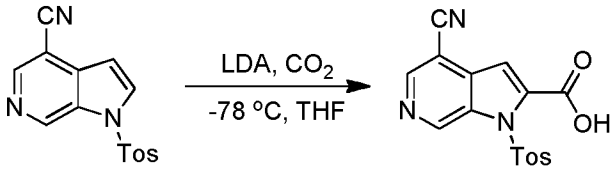


4 5

A mixture of 4-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (4 g, 11.39 mmol, 1 *eq*), $Zn(CN)_2$ (2.67 g, 22.78 mmol, 1.45 mL, 2 *eq*), $Pd(t\text{-}Bu_3P)_2$ (582.04 mg, 1.14 mmol, 0.1 *eq*) in DMF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 hr under N_2 atmosphere. LCMS showed there were no starting material and main desired compound. The mixture was diluted with EtOAc (200 mL). It was washed with aqueous 5% LiCl (80 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica column chromatography (eluent of 0~50% EtOAc/Petroleum ether gradient, 80 g silica column). All fractions found to contain product by

TLC (Petroleum ether:EtOAc = 3:1, Rf = 0.3) were combined and evaporated. Compound 1-(p-tolylsulfonyl)pyrrolo[2,3-c] pyridine-4-carbonitrile (690 mg, 2.09 mmol, 18.34% yield, 90% purity) was obtained as a white solid.

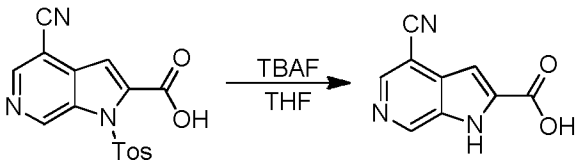
Synthesis of 4-cyano-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid



5 **6**

To a solution of 1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-4-carbonitrile (690 mg, 2.32 mmol, 1 *eq*) in THF (10 mL) was added LDA (2 M, 1.51 mL, 1.3 *eq*) at -78 °C under N_2 atmosphere. The mixture was stirred at -78 °C for 1 h. Then then the mixture was stirred at -78 °C under CO_2 (102.13 mg, 2.32 mmol, 1 *eq*) atmosphere for 0.5 h. LCMS showed there were no starting material and main desired compound. The reaction was quenched at -78 °C with saturated aqueous NH_4Cl (5 mL). There was much white precipitation which was filtered. The cake was dried under reduced pressure. The residue was used directly for next step without further purification. Compound 4-cyano-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid (1.0 g, crude) was obtained as a white solid. LCMS (ESI) m/z 342.0 $[M+H]^+$

Synthesis of 4-cyano-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

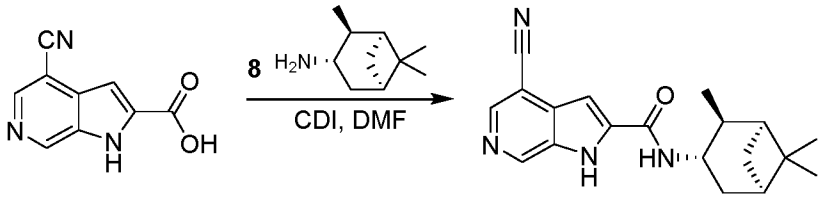


6 **7**

To a solution of 4-cyano-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid (1 g, 2.93 mmol, 1 *eq*) in THF (10 mL) was added TBAF (1 M, 20 mL, 6.83 *eq*). The mixture was stirred at 80 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The mixture was concentrated in reduced pressure. The residue was diluted with H_2O (50 mL). The aqueous phase was extracted with EtOAc (15 mL x 3). The combined organic phase was

washed with saturated brine (10 mL x 2). The residue was used directly for next step without further purification. Compound 4-cyano-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (210 mg, 1.01 mmol, 34.47% yield, 90% purity) was obtained as a white solid. LCMS (ESI) m/z 188.0 $[M+H]^+$

Synthesis of 4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- yrrolo[2,3-c]pyridine-2-carboxamide



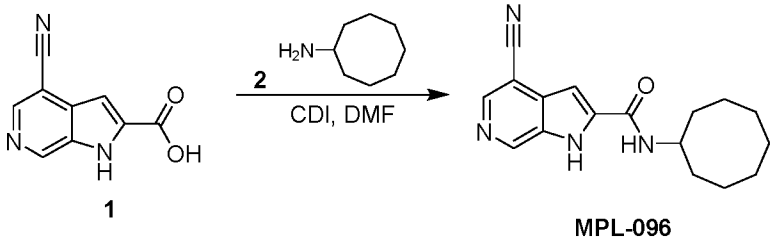
7 **MPL-095**

To a solution of 4-cyano-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 320.59 umol, 1 *eq*) in DMF (1 mL) was added CDI (51.98 mg, 320.59 umol, 1 *eq*). The mixture was stirred at 30 °C for 0.5 h. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (63.88 mg, 416.77 umol, 1.3 *eq*) was added and the mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was purified by prep-HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 45%-75%,11min). Compound 4-cyano-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (20 mg, 62.03 umol, 19.35% yield, 100% purity) was obtained as a white solid which was confirmed by LCMS and ^1H NMR.

LCMS (ESI) m/z 323.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.78 (br s, 1H), 9.00 (s, 1H), 8.76 (br d, *J*=8.8 Hz, 1H), 8.64 (s, 1H), 7.53 (s, 1H), 7.54 - 7.51 (m, 1H), 4.38 (br d, *J*=9.2 Hz, 1H), 2.45 - 2.34 (m, 2H), 2.08 (br t, *J*=6.4 Hz, 1H), 1.94 (br s, 1H), 1.82 (br d, *J*=6.1 Hz, 1H), 1.74 - 1.67 (m, 1H), 1.22 (s, 3H), 1.19 (d, *J*=9.2 Hz, 1H), 1.07 - 1.04 (m, 6H).

Example 70. MPL-096

Synthesis of 4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

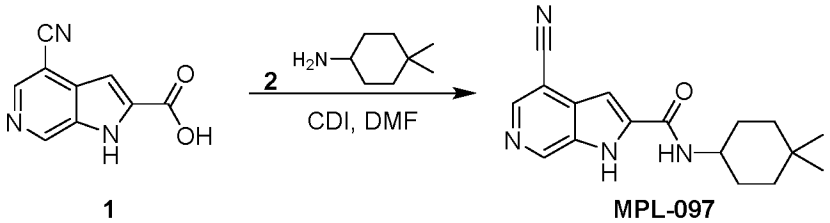


To a solution of 4-cyano-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 534.32 umol, 1 *eq*) in DMF (1 mL) was added CDI (112.63 mg, 694.61 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. Cyclooctanamine (1.92 g, 15.09 mmol, 28.25 *eq*) was added and the reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc (50 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 45%-72%,11min). Then it was purified by preparative TLC(Petroleum ether:EtOAc = 1:1, R_f = 0.3). Compound 4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine -2-carboxamide (10 mg, 33.74 umol, 6.31% yield, 100% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 297.2 $[M+H]^+$; 1H NMR (400MHz, CDCl3-*d*) 10.71 (br s, 1H), 9.08 (s, 1H), 8.64 (s, 1H), 7.03 (s, 1H), 6.39 (br d, *J*=7.0 Hz, 1H), 4.34 - 4.21 (m, 1H), 2.05 -1.96(m, 2H), 1.75 (br d, *J*=9.2 Hz, 4H), 1.69 - 1.62 (m, 8H).

Example 71. MPL-097

Synthesis of 4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide

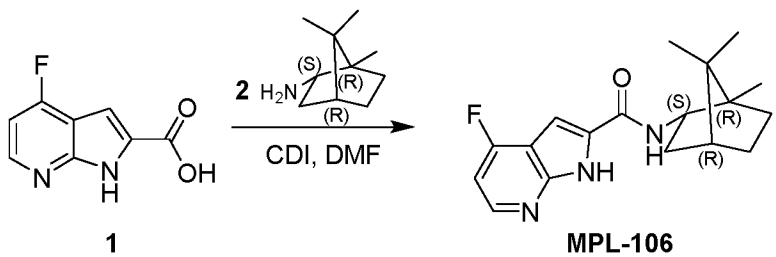


To a solution of 4-cyano-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 320.59 umol, 1 *eq*) in DMF (1 mL) was added CDI (67.58 mg, 416.77 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. 4,4-dimethylcyclohexanamine (53.02 mg, 416.77 umol, 1.3 *eq*) was added and the reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc (50 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 42%-68%,11min) Compound 4-cyano-N-(4,4-dimethylcyclohexyl) -1H-pyrrolo[2,3-c]pyridine-2-carboxamide (15 mg, 49.44 umol, 15.42% yield, 97.69% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 297.2 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ =12.78 (br s, 1H), 9.00 (s, 1H), 8.70 - 8.62 (m, 2H), 7.48 (s, 1H), 7.51 - 7.45 (m, 1H), 7.51 - 7.45 (m, 1H), 3.83 - 3.69 (m, 1H), 3.83 - 3.69 (m, 1H), 1.68 (br d, *J*=9.6 Hz, 2H), 1.61 - 1.48 (m, 2H), 1.45 - 1.37 (m, 2H), 1.33 - 1.23 (m, 2H), 0.93 (d, *J*=9.2 Hz, 5H), 0.97 - 0.89 (m, 1H).

Example 72. MPL-106

Synthesis of 4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



1 **MPL-106**

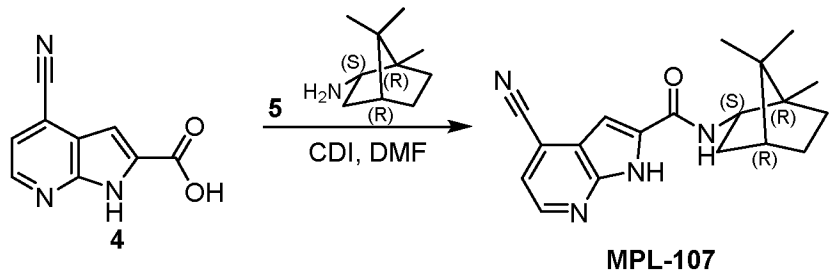
To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (2 mL) was added CDI (108.02 mg, 666.16 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 1,7,7-trimethylnorbornan-2-amine (102.10 mg, 666.16 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for another 0.5 h. LC-MS showed the starting

material 3 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to remove the DCM, and added to water (20 mL), filtered. The filter cake was washed with 10 mL of water, dried under reduced pressure to give the product. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 1:0 to 200:1). The product 4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (112.3 mg, 356.07 umol, 64.14% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 316.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.50 (br s, 1H), 8.33 (dd, *J*=5.5, 8.2 Hz, 1H), 8.12 (br d, *J*=8.5 Hz, 1H), 7.37 (d, *J*=1.8 Hz, 1H), 7.02 (dd, *J*=5.3, 10.4 Hz, 1H), 4.38 (br s, 1H), 2.20 (br s, 1H), 1.82 - 1.64 (m, 3H), 1.40 (br d, *J*=10.1 Hz, 1H), 1.27 (br s, 1H), 1.14 (dd, *J*=4.7, 13.0 Hz, 1H), 0.96 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

Example 73. MPL-107

Synthesis of 4-cyano-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



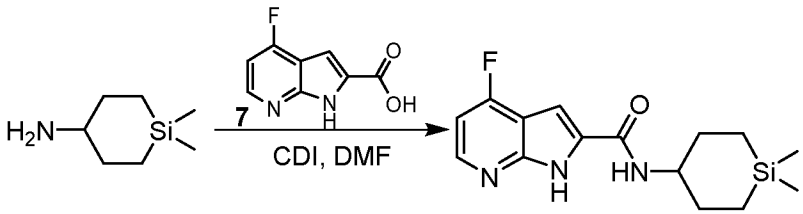
MPL-107

To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (110 mg, 587.75 umol, 1 *eq*) in DMF (2 mL) was added CDI (114.36 mg, 705.30 umol, 1.2 *eq*), the mixture was stirred at 30 °C for 0.5h, then 1,7,7-trimethylnorbornan-2-amine (108.10 mg, 705.30 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for another 0.5 h. LC-MS showed the starting material 4 was consumed completely and one main peak with desired mass was detected. The mixture was added to water(20 mL), filtered. The filter cake was washed with 10 mL of water, dried under reduced pressure to give 4-cyano-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (129.2 mg, 400.74 umol, 68.18% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 323.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.80 (br s, 1H), 8.52 (d, *J*=4.7 Hz, 1H), 8.32 (br d, *J*=8.2 Hz, 1H), 7.64 (d, *J*=4.7 Hz, 1H), 7.57 (s, 1H), 4.40 (br s, 1H), 2.26 - 2.17 (m, 1H), 1.82 - 1.64 (m, 3H), 1.45 - 1.37 (m, 1H), 1.28 (br t, *J*=11.8 Hz, 1H), 1.17 (dd, *J*=4.6, 12.8 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

Example 74. MPL-109

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



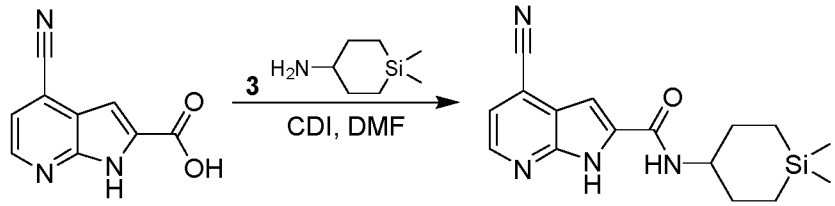
6 **MPL-109**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 277.57 umol, 1 *eq*) in DMF (2 mL) was added CDI (67.51 mg, 416.35 umol, 1.5 *eq*), the mixture was stirred at 30°C for 0.5h, then 1,1-dimethylsilinan-4-amine (59.66 mg, 416.35 umol, 1.5 *eq*) was added and the mixture was stirred at 30 °C for another 0.5 h. LC-MS showed the starting material 6 was consumed completely and one main peak with desired mass was detected. The mixture was added to water (20 mL), and stirred for 10min, filtered. The filter cake was dried under reduced pressure to give the crude product. The product N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (40.3 mg, 122.81 umol, 44.24% yield, 93.072% purity) was obtained as white solid.

LCMS (ESI) m/z 306.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.43 (br s, 1H), 8.32 (dd, *J*=5.4, 8.3 Hz, 2H), 7.22 (s, 1H), 7.00 (dd, *J*=5.4, 10.3 Hz, 1H), 3.78 - 3.66 (m, 1H), 1.99 (br s, 2H), 1.59 (br d, *J*=13.4 Hz, 2H), 0.78 (br d, *J*=14.4 Hz, 2H), 0.66 - 0.55 (m, 2H), 0.12 - 0.01 (m, 6H).

Example 75. MPL-110

Synthesis of 4-cyano-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



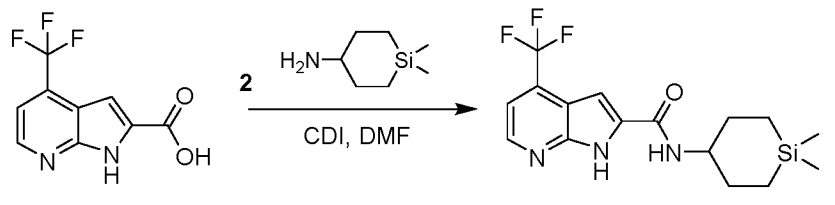
2 MPL-110

To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (600.00 mg, 3.21 mmol, 9.69e-1 *eq*) in DMF (6 mL) was added CDI (804.70 mg, 4.96 mmol, 1.5 *eq*), the mixture was stirred at 25 °C for 0.5 h, then 1,1-dimethylsilinan-4-amine (711.16 mg, 4.96 mmol, 1.5 *eq*) was added. The mixture was stirred at 25 °C for 0.5 h. LCMS (in MeOH) showed the reaction was consumed. The mixture was dropwise added to water (50mL), and stirred for 10min, filtered. The filter cake was dried under reduced pressure to give the crude product. The product 4-cyano-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (705.1 mg, 2.19 mmol, 66.18% yield, 97.026% purity) was obtained as white solid.

LCMS (ESI) m/z 313.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.84 (br s, 1H), 8.51 (br d, *J*=4.9 Hz, 2H), 7.63 (d, *J*=4.6 Hz, 1H), 7.41 (s, 1H), 3.73 (br d, *J*=8.1 Hz, 1H), 2.01 (br d, *J*=9.8 Hz, 2H), 1.68 - 1.54 (m, 2H), 0.84 - 0.75 (m, 2H), 0.62 (dt, *J*=4.5, 14.1 Hz, 2H), 0.12 - 0.01 (m, 6H).

Example 76. MPL-111

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



1 MPL-111

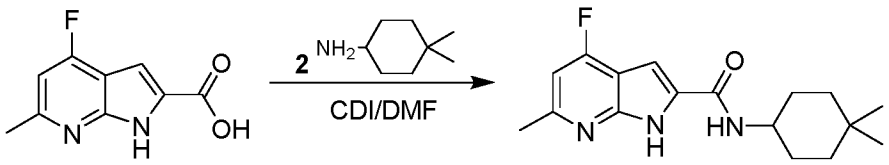
To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (0.2 g, 869.02 umol, 1 *eq*) in DMF (5 mL, dried by CaH_2) was added CDI (183.18 mg, 1.13 mmol, 1.3 *eq*). The

mixture was stirred at 15 °C for 0.5 hr. Then 1,1-dimethylsilinan-4-amine (161.89 mg, 1.13 mmol, 1.3 *eq*) was added. The mixture was stirred at 15 °C further 1 hr. LC-MS showed reactant was consumed completely and desired mass was detected. The reaction mixture was mixed into water (50mL). Filtered, the filtered cake was washed with water (10mL *2) Compound N-(1,1-dimethylsilinan-4-yl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (258.7 mg, 705.96 umol, 81.24% yield, 96.992% purity) was obtained as a white solid.

LCMS (ESI) m/z 355.13 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.59 (br s, 1 H) 8.45 (d, *J*=4.73 Hz, 1 H) 8.41 (d, *J*=8.24 Hz, 1 H) 7.38 (d, *J*=4.88 Hz, 1 H) 7.24 (d, *J*=1.53 Hz, 1 H) 3.59 - 3.67 (m, 1 H) 1.92 (br dd, *J*=9.23, 3.59 Hz, 2 H) 1.46 - 1.56 (m, 2 H) 0.69 (br d, *J*=14.50 Hz, 2 H) 0.53 (td, *J*=14.19, 4.73 Hz, 2 H) 0.00 (s, 3 H) -0.07 --0.03 (m, 3 H).

Example 77. MPL-118

Synthesis of N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



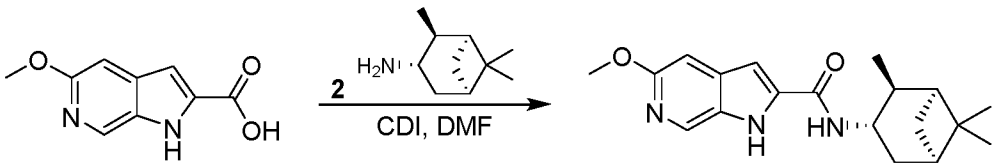
1 **MPL-118**

To a solution of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (60 mg, 309.02 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (60.13 mg, 370.82 umol, 1.2 *eq*), the mixture was stirred at 30 °C for 0.5 h, then 4,4-dimethylcyclohexanamine (47.18 mg, 370.82 umol, 1.2 *eq*) was added, the mixture was stirred at 30 °C for another 0.5 h. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was added to water (20mL), filtered and the filter cake was washed with 10 mL x 3 of petroleum ether, dried under reduced pressure to give the crude product. The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 50%-80%,11min). The product N-(4,4-dimethylcyclohexyl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (23.6 mg, 76.58 umol, 24.78% yield, 98.445% purity) was obtained as white solid.

LCMS (ESI) m/z 304.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.23 (br s, 1H), 8.24 (d, *J*=7.9 Hz, 1H), 7.17 (d, *J*=2.2 Hz, 1H), 6.89 (d, *J*=11.4 Hz, 1H), 3.72 (br d, *J*=7.9 Hz, 1H), 2.53 (s, 3H), 1.67 (br d, *J*=9.6 Hz, 2H), 1.51 (br d, *J*=12.3 Hz, 2H), 1.45 - 1.38 (m, 2H), 1.32 - 1.23 (m, 2H), 0.93 (d, *J*=7.9 Hz, 6H).

Example 78. MPL-120

Synthesis of 5-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-c]pyridine-2-carboxamide

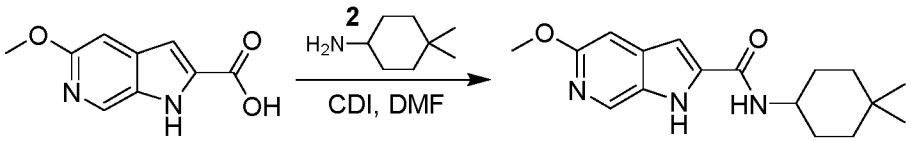


To a solution of 5-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 520.37 umol, 1 *eq*) in DMF (1 mL) was added CDI (109.69 mg, 676.48 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (103.68 mg, 676.48 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 34%-64%,11min). Compound 5-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide (40 mg, 117.87 umol, 22.65% yield, 96.48% purity) was obtained as a white solid.

LCMS (ESI) m/z 328.2 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ = 11.97 (br s, 1H), 8.61 (br d, *J*=8.3 Hz, 1H), 8.42 (s, 1H), 7.13 (s, 1H), 7.11 - 7.07 (m, 1H), 7.09 (s, 1H), 4.36 (quin, *J*=8.1Hz, 1H), 3.87 (s, 3H), 2.39 - 2.32 (m, 1H), 2.41 (br s, 1H), 2.11 - 2.02 (m, 1H), 1.92 (br s, 1H), 1.79 (br t, *J*=5.4 Hz, 1H), 1.73 - 1.64 (m, 1H), 1.68 (br dd, *J*=6.5, 11.9 Hz, 1H), 1.24 - 1.16 (m, 4H), 1.07 - 1.01 (m, 6H).

Example 79. MPL-121

Synthesis of N-(4,4-dimethylcyclohexyl)-5-methoxy-1H-pyrrolo[2,3-c]pyridine-2- carboxamide



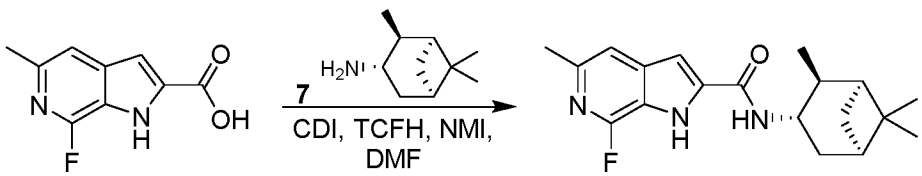
1 MPL-121

To a solution of 5-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 520.37 umol, 1 *eq*) in DMF (1 mL) was added CDI (109.69 mg, 676.48 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5. Then 4,4-dimethylcyclohexanamine (86.07 mg, 676.48 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was delivered without further purification. Compound N-(4,4-dimethylcyclohexyl)-5-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (80 mg, 253.71 umol, 48.76% yield, 95.58% purity) was obtained as a yellow solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 302.2 $[M+H]^+$; 1H NMR (400MHz, DMSO-d_6) δ = 11.71 (br s, 1H), 8.46 - 8.29 (m, 2H), 7.01 (s, 1H), 6.91 (s, 1H), 3.81 (s, 3H), 3.72 (br d, *J*=8.8 Hz, 1H), 3.76 - 3.66 (m,1H), 1.64 (br d, *J*=9.2 Hz, 2H), 1.58 - 1.46 (m, 2H), 1.42 - 1.35 (m, 2H), 1.30 - 1.22 (m, 2H), 0.93 (s, 3H), 0.91 (s,3H).

Example 80. MPL-122

Synthesis of 7-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo [2,3-c]pyridine-2-carboxamide



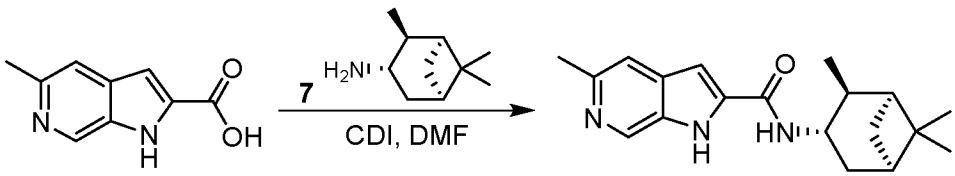
6 MPL-122

To a solution of 7-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 206.01 umol, 1 *eq*) in DMF (1 mL) was added CDI (43.43 mg, 267.82 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (37.89 mg, 247.22 umol, 1.2 *eq*) was added and the mixture was stirred at 30 °C for 12 h. LCMS showed there were starting material and main desired compound. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (16 mg, 0.6 eq) was added and the mixture was stirred at 30°C for another 12 hr. LCMS showed there were starting material and main desired compound. [chloro(dimethylamino)methylene]-dimethyl- ammonium;hexafluorophosphate (75.14 mg, 267.82 umol, 1.3 *eq*) and 1-methylimidazole (50.74 mg, 618.04 umol, 49.27 uL, 3 *eq*) was added and the mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. TLC (SiO_2, Petroleum ether:EtOAc = 2:1, R_f = 0.3). Compound 7-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide (15 mg, 45.44 umol, 22.05% yield, 99.78% purity) was obtained as a white solid.

LCMS (ESI) m/z 330.2 $[M+H]^+$; ^{1}H NMR (500MHz, CHLOROFORM-d) 10.08 (br s, 1H), 7.20 (d, *J*=2.7 Hz, 1H), 6.77 (s, 1H), 6.13 (br d, *J*=8.5 Hz, 1H), 4.59 - 4.52 (m, 1H), 2.79 - 2.69 (m,1H), 2.53 (s, 3H), 2.51 - 2.45 (m, 1H), 2.05 - 2.00 (m, 1H), 1.96 - 1.87 (m, 2H), 1.68 (br dd, *J*=2.1, 6.2 Hz, 1H), 1.26 (s, 3H), 1.19 (d, *J*=7.0 Hz, 3H), 1.11 (s,3H), 0.93 (d, *J*=10.1 Hz, 1H).

Example 81. MPL-124

Synthesis of 5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



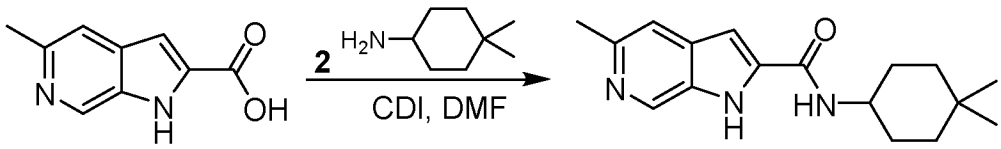
6 **MPL-124**

To a solution of 5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (120 mg, 272.46 umol, 1 *eq*) in DMF (1 mL) was added CDI (66.27 mg, 408.69 umol, 1.5 *eq*). The mixture was stirred at 30 °C for 0.5 h. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (62.64 mg, 408.69 umol, 1.5 *eq*) was added and the mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (10 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The crude product was purified by silica column chromatography (eluent of 50~100% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 0:1, Rf = 0.3) were combined and evaporated. Compound 5-methyl-N-[(1S,2S,3S,5R)- 2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (30 mg, 94.91 umol, 34.83% yield, 98.52% purity) was obtained as a white solid.

LCMS (ESI) m/z 312.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 11.88 (br s, 1H), 8.67 (s, 1H), 8.55 (br d, *J*=8.5 Hz, 1H), 7.43 (s, 1H), 7.13 (s, 1H), 4.39 (quin, *J*=8.1 Hz, 1H), 2.47 - 2.41 (m,1H), 2.37 (br d, *J*=6.7 Hz, 1H), 2.08 (br t, *J*=7.1 Hz, 1H), 1.95 (br s, 1H), 1.81 (br t, *J*=5.2 Hz, 1H), 1.71 (br dd, *J*=6.0, 12.8 Hz, 1H), 1.25 - 1.19 (m, 4H),1.08 - 1.04 (m, 6H).

Example 82. MPL-125

Synthesis of N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2- carboxamide



1 **MPL-125**

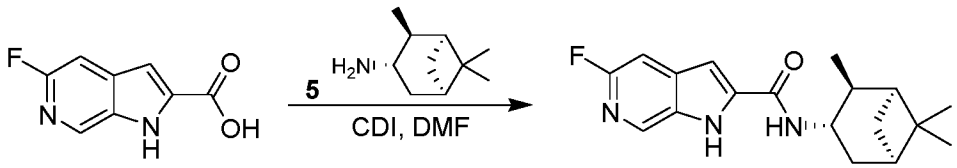
To a solution of 5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (200 mg, 454.10 umol, 1 *eq*) in DMF (1 mL) was added CDI (95.72 mg, 590.33 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. 4,4-dimethylcyclohexanamine (75.11 mg, 590.33 umol, 1.3 *eq*) was added and the mixture was stirred at 30 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (5 mL), dried with

anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The crude product was purified by silica column chromatography (eluent of 50~100% EtOAc /Petroleum ether gradient, 12 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 0:1, Rf = 0.2) were combined and evaporated. Compound N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (15 mg, 50.31 umol, 11.08% yield, 95.72% purity) was obtained as a white solid.

LCMS (ESI) m/z 286.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 11.86 (br s, 1H), 8.64 (s, 1H), 8.43 (br d, *J*=8.1 Hz, 1H), 7.41 (s, 1H), 7.07 (s, 1H), 3.74 - 3.70 (m, 1H), 2.48 (br s, 3H),1.65 (br d, *J*=10.7 Hz, 2H), 1.57 - 1.47 (m, 2H), 1.39 (br d, *J*=12.7 Hz, 2H), 1.30 - 1.21 (m, 2H), 0.92 (br d, *J*=10.7 Hz, 6H).

Example 83. MPL-128

Synthesis of 5-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



4 **MPL-128**

To a solution of 5-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (70 mg, 388.60 umol, 1 *eq*) in DMF (1 mL) was added CDI (81.91 mg, 505.17 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (77.42 mg, 505.17 umol, 1.3 *eq*) was added. The reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were main starting material and desired compound. (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (38.5 mg, 0.5 eq) was added. The mixture was stirred at 30 °C for another 12 h. LCMS showed there was no starting material and mian desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL) and concentrated in reduced pressure. The crude product was purified by silica column chromatography (eluent of 0~40% EtOAc /Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum

ether:EtOAc = 3:1, Rf = 0.3) were combined and evaporated. Compound 5-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan -3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (50 mg, 158.24 umol, 40.72% yield, 99.81% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 316.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.13 (s, 1H), 8.63 (d, J=8.7 Hz, 1H), 8.38 (s, 1H), 7.32 (s, 1H), 7.24 (s, 1H), 4.38 (quin, J=8.1 Hz, 1H), 2.44 (br t, J=11.9Hz, 1H), 2.37 (q, J=6.7 Hz, 1H), 2.08 (quin, J=7.2 Hz, 1H), 1.95 (br s, 1H), 1.81 (t, J=5.8 Hz, 1H), 1.71 (br dd, J=6.5, 12.7 Hz, 1H), 1.23 (s, 3H), 1.21 (d,J=9.6 Hz, 1H), 1.08 - 1.04 (m, 6H).

Example 84. MPL-129

Synthesis of N-(4,4-dimethylcyclohexyl)-5-fluoro-1H-pyrrolo[2,3-c]pyridine-2- carboxamide

1 MPL-129

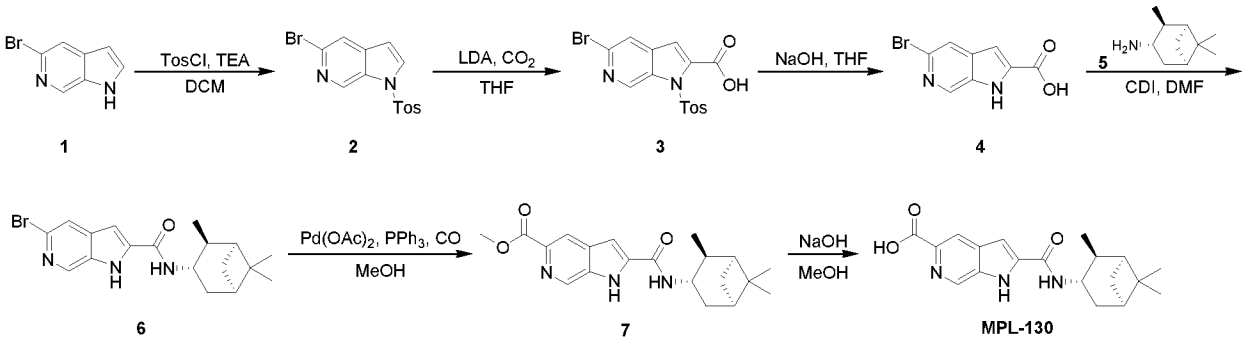
To a solution of 5-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 333.08 umol, 1 *eq*) in DMF (1 mL) was added CDI (70.21 mg, 433.01 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 4,4-dimethylcyclohexanamine (55.09 mg, 433.01 umol, 1.3 *eq*) was added. The reaction mixture was stirred at 30 °C for 12 h. LCMS showed there were main starting material and desired compound. 4,4-dimethylcyclohexanamine (28 mg, 0.5 eq) was added. The mixture was stirred at 30 °C for another 12 h. LCMS showed no starting material but one major product. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by silica column chromatography (eluent of 0~50% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 3:1, Rf = 0.3) were combined and evaporated. Then the crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 50*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 47%-75%,11min). Compound N-(4,4-dimethylcyclohexyl)-5-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (50 mg, 172.80 umol,

51.88% yield, 100% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

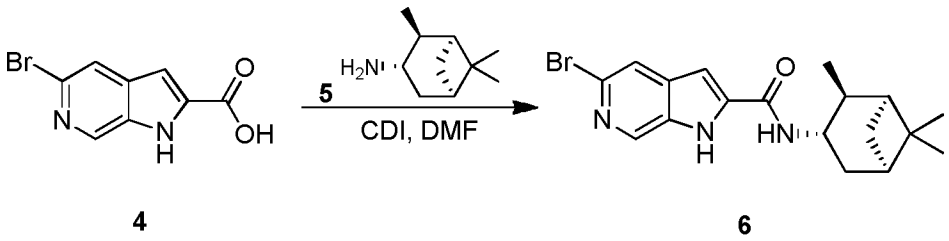
LCMS (ESI) m/z 290.1 $[M+H]^+$; 1H NMR (500MHz, CHLOROFORM-d) 10.39 (br s, 1H), 8.51 (s, 1H), 7.11 (s, 1H), 6.80 (s, 1H), 6.21 (br d, *J*=7.8 Hz, 1H), 4.03 - 3.95 (m, 1H), 1.97 -1.91 (m, 2H), 1.56 - 1.46 (m, 4H), 1.44 - 1.36 (m, 2H), 0.98 (s, 6H).

Example 85. MPL-130

Scheme



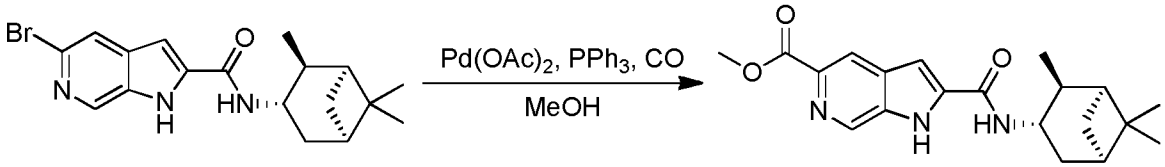
Synthesis of 5-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-3aH-pyrrolo [2,3-c]pyridine-2-carboxamide



To a solution of 5-bromo-3aH-pyrrolo[2,3-c]pyridine-2-carboxylic acid (500 mg, 2.07 mmol, 1 *eq*) in DMF (5 mL) was added CDI (504.53 mg, 3.11 mmol, 1.5 *eq*), the mixture was stirred at 30°C for 0.5 h, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (476.88 mg, 3.11 mmol, 1.5 *eq*) was added and the mixture was stirred for another 0.5 h at the same temperature. LCMS showed the desired mass was detected. The mixture was dropwise added to water (50mL), and stirred for 10min, filtered and the filter cake was dried under reduced pressure to give the crude product. The product 5-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-3aH-

pyrrolo[2,3-c]pyridine-2-carboxamide (750 mg, 1.79 mmol, 86.48% yield, 90% purity) was obtained as white solid.

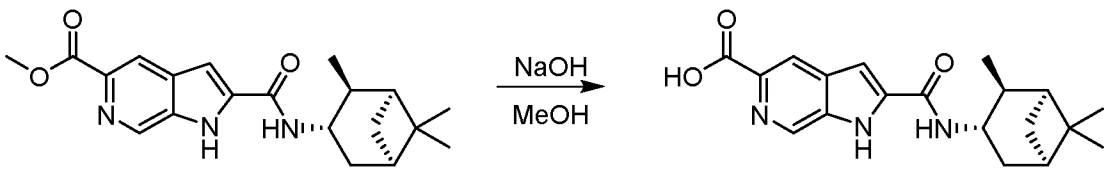
Synthesis of methyl 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H -pyrrolo[2,3-c]pyridine-5-carboxylae



6 7

To a solution of 5-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (450 mg, 1.20 mmol, 1 *eq*) in DMF (2 mL) was added MeOH (2 mL), $Pd(OAc)_2$ (26.85 mg, 119.59 umol, 0.1 *eq*), PPh_3 (62.73 mg, 239.18 umol, 0.2 *eq*) and TEA (605.06 mg, 5.98 mmol, 832.27 uL, 5 *eq*). The mixture was evacuated 3 times with CO and stirred at 80°C for 108 hr under carbon monoxide in 3 atm. LC-MS showed one peak with desired mass was detected and the reactant 6 was consumed completely. The mixture was filtered and the filter was concentrated under reduced pressure to give a residue. The residue was used directly for the next step without purification. The crude product methyl 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylae (400 mg, 1.13 mmol, 94.11% yield) was obtained as brown solid and was used directly for the next step without purification.

Synthesis of 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo [2,3-c]pyridine-5-carboxylic acid



7 MPL-130

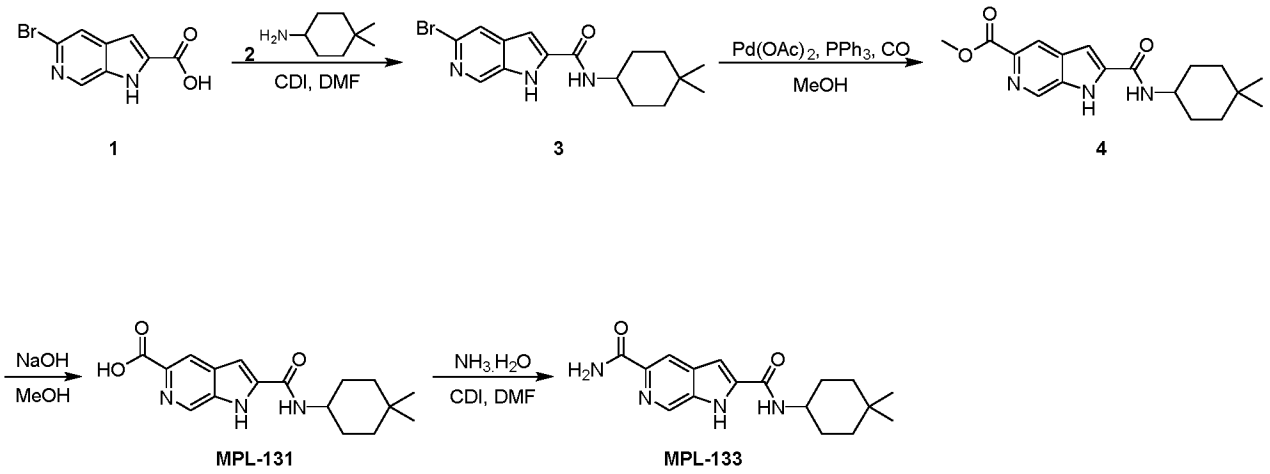
To a solution of methyl 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo [2,3-c]pyridine-5-carboxylate (400 mg, 1.13 mmol, 1 *eq*) in MeOH (5 mL) was added LiOH (2

M, 4.26 mL, 7.56 *eq*) (in water), the mixture was stirred at 25 °C for 12 hr. LC-MS showed the starting material 7 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue, extracted with EtOAc(20Ml x 2). The combined inorganic layers were concentrated under reduced pressure to give a residue(2 mL). The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30 5u;mobile phase: [water(0.225%FA)-ACN];B%: 30%-56%,11min). The product 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid (5.2 mg, 14.70 umol, 1.31% yield, 96.482% purity) was obtained as brown solid.

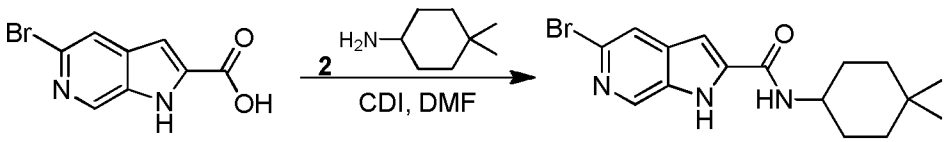
LCMS (ESI) m/z 342.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.60 (br s, 1H), 8.83 (s, 1H), 8.75 (br d, *J*=8.3 Hz, 1H), 8.51 (s, 1H), 7.46 (s, 1H), 4.41 (br t, *J*=8.4 Hz, 1H), 2.45 (br s, 2H), 2.10 (br t, *J*=7.2 Hz, 1H), 1.96 (br s, 1H), 1.82 (br t, *J*=5.3 Hz, 1H), 1.73 (br dd, *J*=7.2, 12.6 Hz, 1H), 1.25 - 1.20 (m, 4H), 1.09 - 1.04 (m, 6H).

Examples 86 and 87. MPL-131 and MPL-133

Scheme



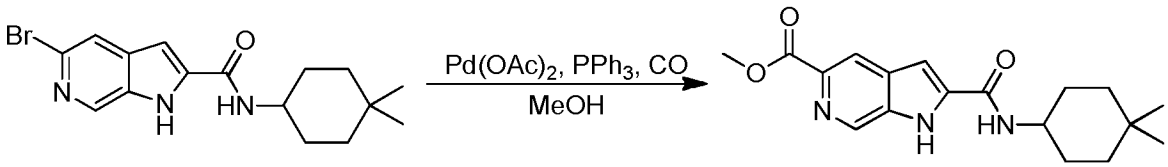
Synthesis of 5-bromo-N-(4,4-dimethylcyclohexyl)-3aH-pyrrolo[2,3-c]pyridine- 2-carboxamide



1 3

To a solution of 5-bromo-3aH-pyrrolo[2,3-c]pyridine-2-carboxylic acid (500 mg, 2.07 mmol, 1 *eq*) in DMF (5 mL) was added CDI (504.53 mg, 3.11 mmol, 1.5 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 4,4-dimethylcyclohexanamine (395.87 mg, 3.11 mmol, 1.5 *eq*) was added and the mixture was stirred for another 0.5 h at the same temperature. LCMS showed the desired mass was detected and the reactant 1 was consumed. The mixture was concentrated under reduced pressure to give a residue, then diluted with water (30 mL), acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 10 mL x3 of Petroleum ether, dried under reduced pressure to give the product. The crude product was used directly for the next step without purification. The product 5-bromo-N-(4,4-dimethylcyclohexyl)-3aH-pyrrolo[2,3-c] pyridine-2-carboxamide (550 mg, 1.56 mmol, 75.37% yield, 99.563% purity) was obtained as brown solid. LCMS (ESI) m/z 350.0 $[M]^+$

Synthesis of 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine- 5-carboxylate

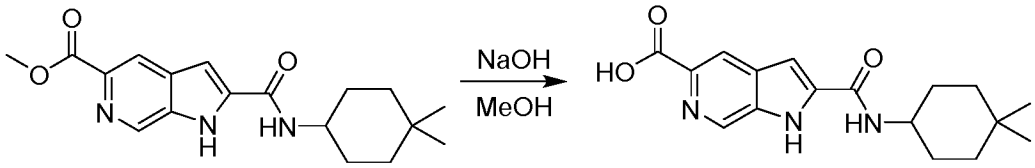


3 4

To a solution of 5-bromo-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (550 mg, 1.57 mmol, 1 *eq*) in DMF (3 mL) was added MeOH (3 mL), $Pd(OAc)_2$ (35.25 mg, 157.03 umol, 0.1 *eq*), PPh_3 (82.37 mg, 314.06 umol, 0.2 *eq*) and TEA (794.49 mg, 7.85 mmol, 1.09 mL, 5 *eq*). The mixture was evacuated 3 times with CO and stirred at 80 °C for 108 hr under carbon monoxide in 3atm. LC-MS showed one peak with desired mass was detected and the reactant 3 was consumed. The mixture was filtered and the filter was concentrated under reduced pressure to give a residue. The residue was used directly for the next step without purification. The crude product methyl 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-

c] pyridine-5-carboxylate (500 mg, 1.52 mmol, 96.67% yield) was obtained as brown solid and was used directly for the next step without purification. LCMS (ESI) m/z 330.1 $[M+H]^+$

Synthesis of 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine- 5-carboxylic acid

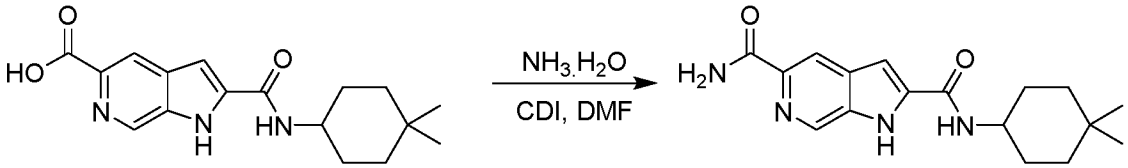


4 **MPL-131**

To a solution of methyl 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine- 5-carboxylate (500 mg, 1.52 mmol, 1 *eq*) (the crude product contained 5-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide 50 mg) in MeOH (5 mL) was added LiOH (2 M, 5.74 mL, 7.56 *eq*) (in water). The mixture was stirred at 25 °C for 12 hr. LC-MS showed the starting material 4 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to give a residue, extracted with EtOAc (20 mL x 2), and the combined inorganic layers were concentrated under reduced pressure to give a residue (2 mL). The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 27%-51%,11min) and prep-HPLC(column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.05%HCl)-ACN];B%: 19%-49%,10min). The product 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid (5 mg, 15.84 umol, 1.04% yield, 99.903% purity) was obtained as white solid. Purity comes from LCMS, and the product was confirmed by H NMR. And the product 2 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid (350 mg, 1.11 mmol, 73.11% yield) was obtained as white solid.

^{1}H NMR (400MHz, DMSO-d_6) δ = 13.17 (br s, 1H), 8.90-8.83 (m, 2H), 8.71 (s, 1H), 7.58 (s, 1H), 3.78 (br d, J=7.4 Hz, 1H), 1.73-1.65 (m, 2H), 1.63-1.51 (m, 2H), 1.47-1.38 (m, 2H), 1.35-1.24 (m, 2H), 0.95 (s, 3H).

Synthesis of N2-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2,5-dicarboxamide



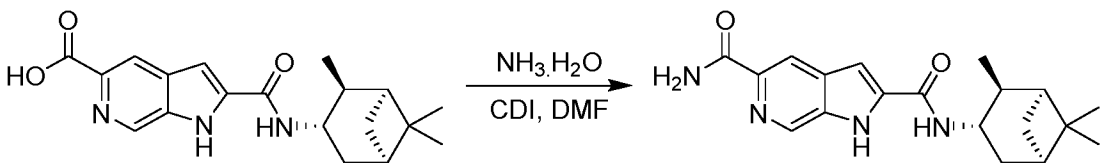
MPL-131 **MPL-133**

To a solution of 2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid (80.00 mg, 253.67 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (61.70 mg, 380.51 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 0.5 h, then $NH_3.H_2O$ (44.45 mg, 380.51 umol, 48.85 uL, 1.5 *eq*) was added. The mixture was stirred at 25 °C for 0.5h. LCMS showed the reaction was consumed and the desired mass was detected. The mixture was added to water (15mL) and stirred for 5min, then filtered and the filter cake was dried under reduced pressure to give the crude product. The crude product was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 31%-54%,11min). The product N2-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2,5-dicarboxamide (19.2 mg, 60.99 umol, 24.04% yield, 99.872% purity) was obtained as white solid. Purity comes from LCMS. The product was confirmed by ^1H NMR.

LCMS (ESI) m/z 315.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.33 (s, 1H), 8.75 (s, 1H), 8.55 (d, *J*=8.1 Hz, 1H), 8.35 (s, 1H), 8.00 (br d, *J*=2.9 Hz, 1H), 7.44 (br d, *J*=2.6 Hz, 1H), 7.34 (d, *J*=1.2 Hz, 1H), 3.81 - 3.72 (m, 1H), 1.67 (br dd, *J*=3.8, 13.3 Hz, 2H), 1.61 - 1.50 (m, 2H), 1.41 (br d, *J*=12.5 Hz, 2H), 1.33 - 1.24 (m, 2H), 0.94 (d, *J*=11.6 Hz, 6H).

Example 88. MPL-132

Synthesis of N2-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2,5-dicarboxamide



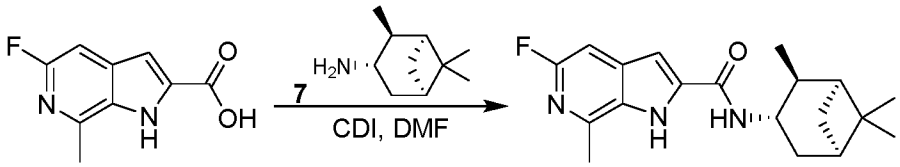
MPL-130 **MPL-132**

To a solution of 2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo [2,3-c]pyridine-5-carboxylic acid (100.00 mg, 292.91 umol, 1 *eq*) in DMF (2 mL) was added CDI (71.24 mg, 439.36 umol, 1.5 *eq*). The mixture was stirred at 25 °Cfor 0.5 h, then $NH_3.H_2O$ (51.33 mg, 439.36 umol, 56.41 uL, 1.5 *eq*) was added. The mixture was stirred at 25 °C for 0.5 h. LCMS showed the reaction was consumed and the desired mass was detected. The reaction mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 36%-63%,11min)without work up. The product N2-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2,5-dicarboxamide (33.1 mg, 97.02 umol, 33.12% yield, 99.783% purity) was obtained as white solid. Purity comes from LCMS. The product was confirmed by ^{1}H NMR.

LCMS (ESI) m/z 341.2 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 8.77 (s, 1H), 8.69 (br d, *J*=8.5 Hz, 1H), 8.40 (s, 1H), 8.06 (br s, 1H), 7.50 (br s, 1H), 7.41 (s, 1H), 4.46 - 4.35 (m, 1H), 2.48 - 2.37 (m, 2H), 2.16 - 2.06 (m, 1H), 1.98 - 1.93 (m, 1H), 1.82 (t, *J*=5.2 Hz, 1H), 1.72 (ddd, *J*=2.1, 6.4, 13.6 Hz, 1H), 1.25 - 1.20 (m, 4H), 1.09 - 1.05 (m, 6H).

Example 89. MPL-134

Synthesis of 5-fluoro-7-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



6 **MPL-134**

To a solution of 5-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 206.01 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (50.11 mg, 309.02 umol, 1.5 *eq*), the mixture was stirred at 30 °C for 0.5 h, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (47.36 mg, 309.02 umol, 1.5 *eq*) was added and the mixture was stirred for another 0.5h at the same temperature. LCMS showed the desired mass was detected. The mixture was dropwise added to water (15 mL), and stirred for 10min, filtered and the filter cake was dried under reduced pressure to give the crude product. The residue was purified by prep-HPLC (column: YMC-

Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 51%-81%,11min). The product 5-fluoro-7-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (23.6 mg, 71.64 umol, 34.78% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 330.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) = 12.05 (s, 1H), 8.57 (d, *J*=8.6 Hz, 1H), 7.18 (d, *J*=1.7 Hz, 1H), 7.09 (s, 1H), 4.39 (br s, 1H), 2.68 (s, 3H), 2.47 - 2.32 (m,2H), 2.08 (s, 1H), 1.94 (br d, *J*=2.4 Hz, 1H), 1.86 - 1.79 (m, 1H), 1.72 (ddd, *J*=2.0, 6.5, 13.6 Hz, 1H), 1.25 - 1.19 (m, 4H), 1.07 (t, *J*=3.5 Hz, 6H).

Example 90. MPL-135

Synthesis of N-(4,4-dimethylcyclohexyl)-5-fluoro-7-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide

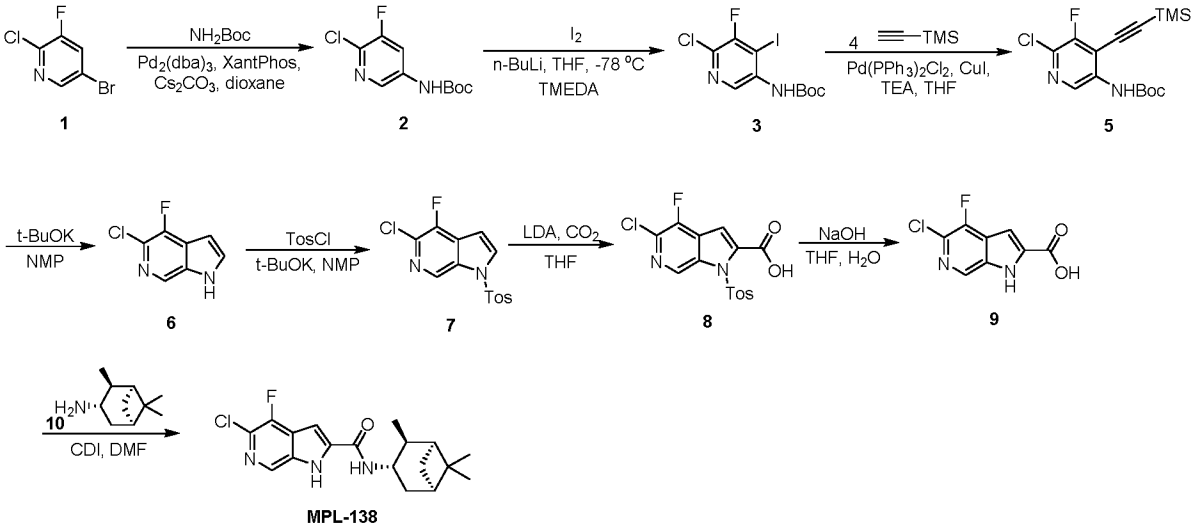
1 **MPL-135**

To a solution of 5-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 257.52 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (62.63 mg, 386.27 umol, 1.5 *eq*). The mixture was stirred at 30 °C for 0.5 h, then 4,4-dimethylcyclohexanamine (49.14 mg, 386.27 umol, 1.5 *eq*) was added. The mixture was stirred for another 0.5 h at the same temperature. LCMS showed the the desired mass was detected. The mixture was dropwise added to water (15 mL), and stirred for 10min, filtered and the filter cake was dried under reduced pressure to give the crude product. The product N-(4,4-dimethylcyclohexyl)-5-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (56.6 mg, 186.57 umol, 72.45% yield, 100% purity) was obtained as white solid.

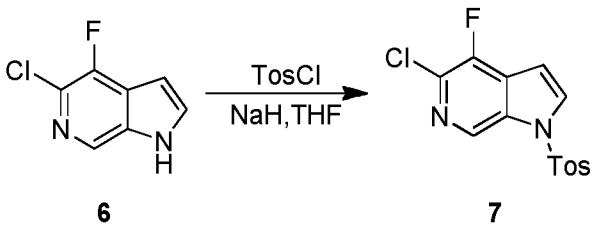
LCMS (ESI) m/z 304.2 $[M+H]^+$; ^1H NMR (400MHz, DMSO-δ_6) =12.02 (br s, 1H), 8.43 (br d, *J*=8.3 Hz, 1H), 7.14 (s, 1H), 7.07 (s, 1H), 3.82 - 3.67 (m, 1H), 2.67 (s, 3H), 1.72 - 1.63 (m, 2H), 1.60 - 1.49 (m, 2H), 1.45 - 1.37 (m, 2H), 1.33 - 1.23 (m, 2H), 0.94 (d, *J*=8.1 Hz, 6H).

Example 91. MPL-138

Scheme



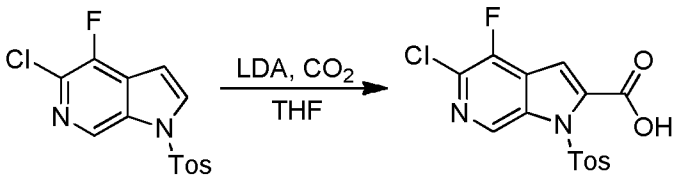
5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine



6 7

To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine (770 mg, 4.51 mmol, 1 *eq*) in THF (10 mL) was added NaH (270.83 mg, 6.77 mmol, 60% purity, 1.5 *eq*). The mixture was stirred at 0 °C for 10 minutes. Then TosCl (1.72 g, 9.03 mmol, 2 *eq*) was added. The mixture was stirred at 25 °C for 12 hr under N_2 atmosphere. TLC and LCMS showed the starting material was consumed completely. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (20 mL). The mixture was concentrated in reduced pressure and diluted with EtOAc (150 mL), The organic phase was washed with brine (50 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by silica column chromatography (0~10% EtOAc/Petroleum ether gradient, 20 g silica column). All fractions were combined and evaporated. Compound 5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (1.1 g, 3.32 mmol, 73.53% yield, 98% purity) was obtained as a yellow solid. LCMS (ESI) m/z 324.9 $[M+H]^+$

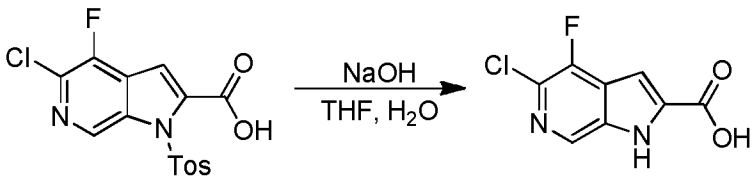
5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2-carboxylic acid



7 **8**

To a solution of 5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine (1.1 g, 3.39 mmol, 1 *eq*) in THF (15 mL) was added LDA (2 M, 2.54 mL, 1.5 *eq*) at -78 °C in 1 hr under N_2 atmosphere. Then, the mixture was stirred in -78 °C under CO_2 (149.07 mg, 3.39 mmol, 1 *eq*) for 0.5 hr. LCMS and TLC showed there were no starting materials and one main peak with desired mass was detected. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) concentrated under reduced pressure to removed THF, then acidified with HCl (2 M) to pH = 5, extracted with EtOAc (20 mL x 3). The mixture was filtered through a Celite pad, and the filtrate cake was concentrated to give the crude product. The crude product was purified by silica column chromatography (eluent of 10~25% EtOAc/Petroleum ether gradient, 20 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 1:1, Rf = 0.2) were combined and evaporated. Compound 5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2 -carboxylic acid (0.98 g, 2.55 mmol, 75.32% yield, 96% purity) was obtained as a white solid. LCMS (ESI) m/z 368.9 $[M+H]^+$

5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

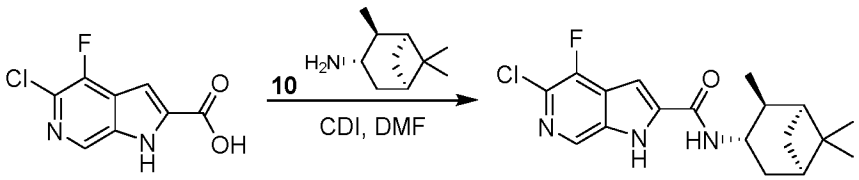


8 **9**

To a solution of 5-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-c]pyridine-2- carboxylic acid (560 mg, 1.52 mmol, 1 *eq*) in NaOH (2 M, 3.50 mL, 4.61 *eq*). and THF (3 mL). The mixture was stirred at 75 °C for 3 hrs. LCMS showed there were no starting materials and main desired compound. The mixture was concentrated under reduced pressure to give a residue, then

acidified with HCl (2 M) to pH = 5. The mixture was filtered through a Celite pad, and the filtrate cake was concentrated to give the crude product. The residue was used directly for next step without further purification. Compound 5-chloro-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2-carboxylic acid (240 mg, 1.12 mmol, 73.65% yield, 100% purity) was obtained as a white solid. LCMS (ESI) m/z 215.0 $[M+H]^+$

5-chloro-4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H– pyrrolo[2,3-c]pyridine-2-carboxamide



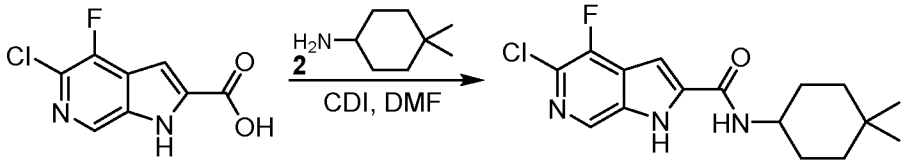
9 **MPL-138**

To a solution of (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (42.85 mg, 279.61 umol, 1.2 *eq*) and CDI (75.56 mg, 466.02 umol, 2 *eq*) was added in DMF (1 mL). The mixture was stirred at 30 °C for 0.5 hr, then 5-chloro-4-fluoro-1H-pyrrolo [2,3-c]pyridine-2-carboxylic acid (50 mg, 233.01 umol, 1 *eq*) was added under N_2 atmosphere. The mixture was stirred at 30 °C for 3 hrs. LCMS showed there was no starting material and main desired compound. The mixture was added in water (10mL) and stirred for 10 mins. The mixture was extracted with EtOAc (15 mL x 3). The organic phase was washed with saturated brine (4 mL x 3). The mixture was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by reversed-phase HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 55%-84%,11min). Compound 5-chloro-4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide (9.2 mg, 25.51 umol, 10.95% yield, 97% purity) was obtained as a white solid.

LCMS (ESI) m/z 350.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ =1.02 - 1.10 (m, 1 H) 1.06 (s, 3 H) 1.19 (br d, *J*=9.54 Hz, 1 H) 1.23 (s, 3 H) 1.71 (br dd, *J*=11.86, 6.24 Hz, 1 H) 1.81 (br t, *J*=5.01 Hz, 1 H) 1.90 - 2.00 (m, 1 H) 2.08 (br t, *J*=7.34 Hz, 1 H) 2.29 - 2.45 (m, 1 H) 2.29 - 2.45 (m, 1 H) 4.29 - 4.47 (m, 1 H) 7.42 (s, 1 H) 8.46 (s, 1 H) 8.70 (br d, *J*=8.56 Hz, 1 H) 12.64 (br s, 1 H).

Example 92. MPL-139

5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine -2-carboxamide



1 **MPL-139**

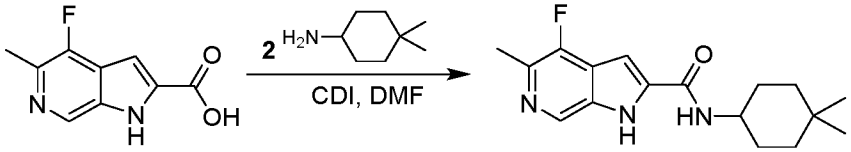
To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 186.41 umol, 1 *eq*) and CDI (60.45 mg, 372.82 umol, 2 *eq*) was added in DMF (1 mL). The mixture was stirred at 25 °C for 0.5 h, then 4,4-dimethylcyclohexanamine (28.46 mg, 223.69 umol, 1.2 *eq*) was added under N_2 atmosphere. The mixture was stirred at 25 °C for 3 h under N_2 atmosphere. LCMS showed starting material consumed and no desired product. The mixture was added in water (10mL) and stirred for 10 mins. The mixture was extracted with EtOAc (15 mL x 3). The organic phase was washed with brine (4 mL x 3). The mixture was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by reverse-phase HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 52%-77%,11min). Compound 5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-1H–pyrrolo[2,3-c]pyridine-2-carboxamide (8.5 mg, 25.99 umol, 13.94% yield, 99% purity) was obtained as a white solid.

LCMS (ESI) m/z 324.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 1.00 - 1.12 (m, 6 H) 1.19 (br d, *J*=9.54 Hz, 1 H) 1.23 (s, 3 H) 1.70 (br dd, *J*=12.10, 6.48 Hz, 1 H) 1.81 (br t, *J*=5.26 Hz,1 H) 1.94 (br s, 1 H) 2.07 (br t, *J*=7.21 Hz, 1 H) 2.30 - 2.45 (m, 2 H) 2.45 - 2.55 (m, 31 H) 4.36 (quin, *J*=8.01 Hz, 1 H) 4.28 - 4.45 (m, 1 H) 7.22 (s, 1 H) 8.48

(s, 1 H) 8.53 (br d, *J*=8.56 Hz, 1 H) 12.54 (br s, 1 H).

Example 93. MPL-141

Synthesis of N-(4,4-dimethylcyclohexyl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide



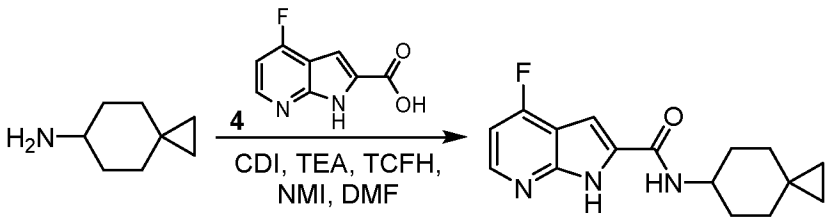
1 MPL-141

To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (0.1 g, 515.03 umol, 1 *eq*) in DMF (5 mL, dried by CaH_2) was added CDI (100.21 mg, 618.04 umol, 1.2 *eq*). The mixture was stirred at 20 °C for 0.5 hr. Then 4,4-dimethylcyclohexanamine (78.63 mg, 618.04 umol, 1.2 *eq*) was added, the mixture was stirred at 20 °C for 1 hr. LC-MS showed Reactant was consumed completely and one main peak with desired mass was detected. The reaction mixture was dropped into water (20mL). The product was isolated as white solid. Filtered, the filter cake was redissolved in DMF (8 mL), and then purified by prep-HPLC (FA condition, column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 30%-55%,11min). Compound N-(4,4-dimethylcyclohexyl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide(18mg, 59.33 umol, 11.52% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 303.17 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 0.95 (d, *J*=10.68 Hz, 6 H) 1.26 - 1.35 (m, 2 H) 1.43 (br d, *J*=12.36 Hz, 2 H) 1.51 - 1.61 (m, 2 H) 1.69 (br dd, *J*=13.12,3.81 Hz, 2 H) 2.49 (d, *J*=3.05 Hz, 3 H) 3.72 - 3.81 (m, 1 H) 7.29 (s, 1 H) 8.53 (br d, *J*=7.93 Hz, 1 H) 8.56 (s, 1 H) 12.38 (br s, 1 H).

Example 94. MPL-154

Synthesis of 4-fluoro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



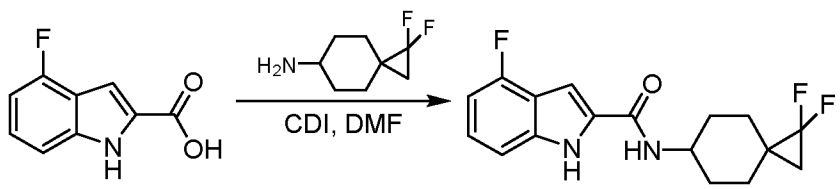
3 MPL-154

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 277.57 umol, 1 *eq*) in DMF (1 mL) was added TEA (84.26 mg, 832.71 umol, 115.90 uL, 3 *eq*) and CDI (58.51 mg, 360.84 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 hr. Spiro[2.5]octan-6-amine (53.85 mg, 333.08 umol, 1.2 *eq*, HCl) was added and the mixture was stirred at 30 °C for another 12 h. LCMS showed there were starting material and main desired compound. [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (101.24 mg, 360.84 umol, 1.3 *eq*) and 1-methylimidazole (68.37 mg, 832.71 umol, 66.38 uL, 3 *eq*) was added and the mixture was stirred at 30 °C for 12 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 10:1 to 1:1). Then the residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 44%-70%,11min). Compound 4-fluoro-N-spiro[2.5]octan-6-yl-1H- pyrrolo[2,3-b]pyridine-2-carboxamide (20 mg, 69.61 umol, 25.08% yield, 100% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 288.1 $[M+H]^+$; ^{1}H NMR (500MHz, METHANOL-d_4) = 8.32 (br t, *J*=6.4 Hz, 1H), 8.35 - 8.28 (m, 1H), 7.22 (s, 1H), 6.94 (br dd, *J*=5.6, 9.7 Hz, 1H), 3.95 (br t, *J*=11.2 Hz,1H), 2.00 - 1.84 (m, 4H), 1.65 - 1.55 (m, 2H), 1.01 (br d, *J*=12.8 Hz, 2H), 0.34 (br d, *J*=7.2 Hz, 2H), 0.30 (br d, *J*=6.7 Hz, 2H).

Example 95. MPL-155

N-(2,2-difluorospiro[2.5]octan-6-yl)-4-fluoro-1H-pyrrolo[2,3-b] pyridine -2-carboxamide



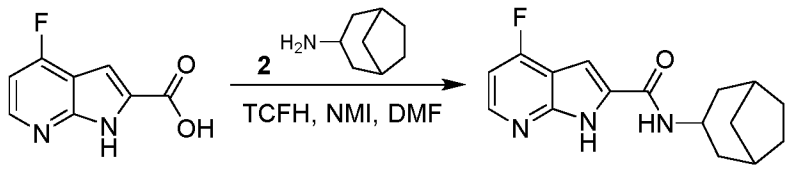
1 **MPL-155**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50.28 mg, 279.10 umol, 1 *eq*) in DMF (1 mL) was added CDI (90.51 mg, 558.20 umol, 2 *eq*) and TEA (56.48 mg, 558.20 umol, 77.69 uL, 2 *eq*) under N_2 atmosphere. The mixture was stirred at 30 °C for 0.5 hr under N_2 atmosphere. Then 2,2-difluorospiro [2.5]octan-6-amine (53.99 mg, 273.24 umol, 9.79e-1 *eq*, HCl) was added. The mixture was stirred at 30 °C for 2 hr under N_2 atmosphere. LCMS showed the starting material was still existed and main desired compound. The mixture was added in water (10 mL) and stirred for 10 mins. The mixture was extracted with EtOAc (15 mL x 3). The organic phase was washed with saturated brine (15 mL x 3). The mixture was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by reversed-phase HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 45%-70%,11min). Compound N-(2,2- difluorospiro [2.5]octan-6-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine -2-carboxamide (7.2 mg, 21.16 umol, 7.58% yield, 95% purity) was obtained as a white solid.

LCMS (ESI) m/z 324.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-*d6*) δ = 1.25 (br t, *J*=8.54 Hz, 2 H) 1.37 - 1.62 (m, 4 H) 1.68 - 1.82 (m, 2 H) 1.89 (br dd, *J*=12.44, 3.28 Hz, 2 H) 3.83 - 3.98 (m,1 H) 7.01 (dd, *J*=10.22, 5.34 Hz, 1 H) 7.27 (d, *J*=1.83 Hz, 1 H) 8.32 (dd, *J*=8.32, 5.42 Hz, 1 H) 8.40 (br d, *J*=7.78 Hz, 1 H) 12.48 (br s, 1 H).

Example 96. MPL-157

Synthesis of N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2- carboxamide



1 **MPL-157**

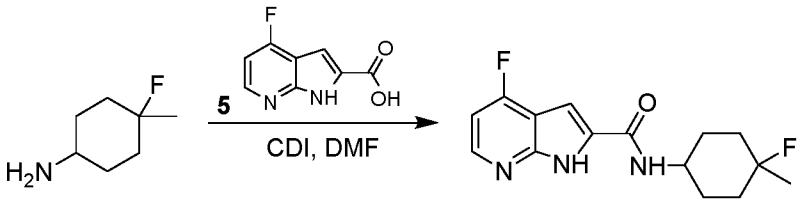
To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30.39 mg, 168.69 umol, 1 *eq*) in DMF (0.5 mL) was added bicyclo[3.2.1]octan-3-amine (30 mg, 185.56 umol, 1.1 *eq*, HCl), 1-methylimidazole (55.40 mg, 674.77 umol, 53.79 uL, 4 *eq*) and [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (61.53 mg, 219.30 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were no

starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was purified by prep. HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 45%-74%,11min). Compound N-(3-bicyclo[3.2.1]octanyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (10 mg, 34.36 umol, 20.37% yield, 98.72% purity) was obtained as a white solid.

LCMS (ESI) m/z 288.1 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d4) 8.31 (dd, *J*=5.7, 7.9 Hz, 1H), 7.18 (s, 1H), 6.92 (dd, *J*=5.5, 9.9 Hz, 1H), 4.34 - 4.22 (m, 1H), 2.30 (br s, 2H), 1.91 -1.83 (m, 2H), 1.78 - 1.65 (m, 4H), 1.53 - 1.42 (m, 4H).

Example 97. MPL-158

Synthesis of 4-fluoro-N-(4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



4 **MPL-158**

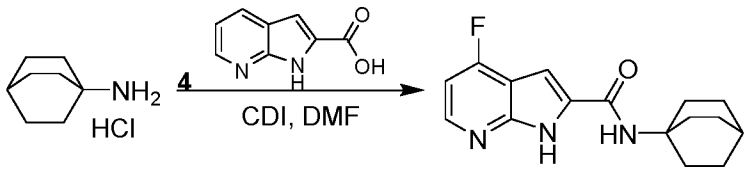
To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added 4-fluoro-4-methyl-cyclohexanamine (120.99 mg, 721.68 umol, 1.3 *eq*, HCl), 1-methylimidazole (227.88 mg, 2.78 mmol, 221.25 uL, 5 *eq*) and [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (233.64 mg, 832.71 umol, 1.5 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 150*30 5u;mobile phase: [water(0.225%FA)-ACN];B%: 45%-70%,11min). Compound 4-fluoro-N-(4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-

b]pyridine-2-carboxamide (40 mg, 133.80 umol, 24.10% yield, 98.11% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI) m/z 294.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.54 - 12.40 (m, 1H), 8.38 - 8.27 (m, 1H), 8.20 (br d, J=7.3 Hz, 1H), 7.23 (d, J=2.0 Hz, 1H), 7.03 - 6.95 (m, 1H), 3.97 -3.94 (m, 0.8H), 3.81 (br s, 0.2H), 1.91 - 1.73 (m, 4H), 1.73 - 1.62 (m, 2H), 1.54 (q, J=8.5 Hz, 2H), 1.39 (s, 1.2H), 1.36 - 1.30 (m, 1.5H), 1.27 (s, 0.3H).

Example 98. MPL-161

Synthesis of N-(4-bicyclo[2.2.2]octanyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2- carboxamide



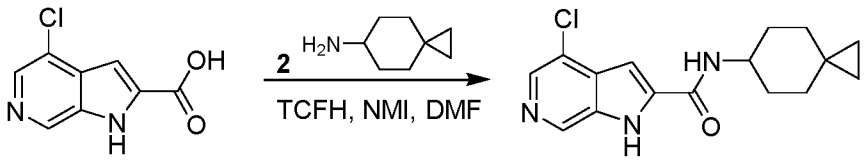
3 **MPL-161**

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 277.57 umol, 1 *eq*) and bicyclo[2.2.2]octan-4-amine (67.31 mg, 416.35 umol, 1.5 *eq*, HCl) in DMF (1 mL) was added HOBt (56.26 mg, 416.35 umol, 1.5 *eq*) and EDCI (79.81 mg, 416.35 umol, 1.5 *eq*) TEA (84.26 mg, 832.71 umol, 115.90 uL, 3 *eq*), the mixture was stirred at 25 °C for 4 hr under N_2. LC-MS showed the starting material 3 was consumed completely and one main peak with desired mass was detected. The mixture was added to water (20mL) and stirred for 10min, filtered and the filter cake was dried under reduced pressure. The product N-(4-bicyclo[2.2.2]octanyl)-4-fluoro-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (68.2 mg, 232.82 umol, 83.88% yield, 98.090% purity) was obtained as a white solid.

LCMS (ESI) m/z 288.1 $[M+H]^+$; ^{1}H NMR (500MHz, METHANOL-d4) = 12.37 (br s, 1H), 8.31 (dd, *J*=5.4, 8.6 Hz, 1H), 7.66 (s, 1H), 7.23 (s, 1H), 6.99 (dd, *J*=5.4, 10.3 Hz, 1H), 1.98 - 1.88 (m, 6H), 1.68 - 1.59 (m, 6H), 1.58 - 1.53 (m, 1H).

Example 99. MPL-163

Synthesis of 4-chloro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



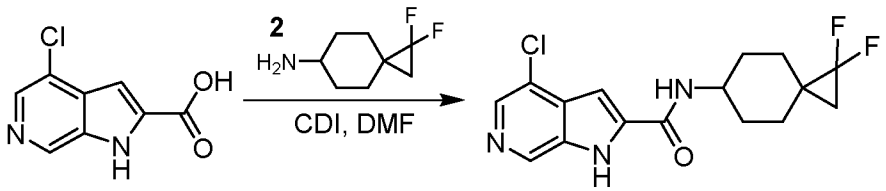
1 MPL-163

To a solution of spiro[2.5]octan-6-amine (53.85 mg, 333.08 umol, 1.2 *eq*, HCl) in DMF (1 mL) was added 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (54.57 mg, 277.57 umol, 1 *eq*), 1-methylimidazole (91.15 mg, 1.11 mmol, 88.50 uL, 4 *eq*) and [chloro(dimethylamino)methylene] -dimethyl-ammonium;hexafluorophosphate (116.82 mg, 416.35 umol, 1.5 *eq*). The mixture was stirred at 30 °C for 12 hr. LCMS showed there were starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in EtOAc (20 mL) and concentrated in vacuo. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 31%-60%,11min). Compound 4-chloro-N-spiro[2.5]octan-6-yl-1H- pyrrolo[2,3-c]pyridine-2-carboxamide (30 mg, 98.32 umol, 35.42% yield, 99.56% purity) was obtained as a white solid.

LCMS (ESI) m/z 304.1 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d4) 8.74 (s, 1H), 8.15 (s, 1H), 7.33 (s, 1H), 4.01 - 3.91 (m, 1H), 1.98 - 1.93 (m, 2H), 1.93 - 1.84 (m, 2H), 1.67 - 1.58 (m,2H), 1.01 (br d, *J*=13.6 Hz, 2H), 0.37 - 0.33 (m, 2H), 0.31 - 0.26 (m, 2H).

Example 100. MPL-164

Synthesis of 4-chloro-N-(1,1-difluorospiro[2.5]octan-6-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



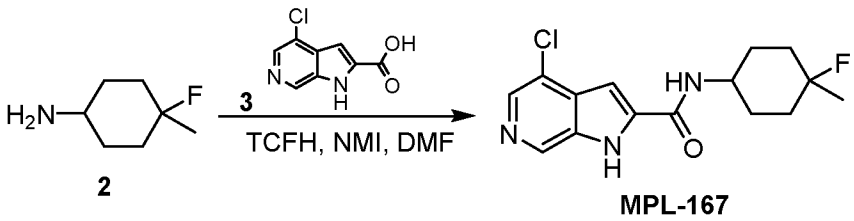
1 MPL-164

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) in DMF (1 mL) was added CDI (49.49 mg, 305.20 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 hr. 2,2-difluorospiro[2.5]octan-6-amine (60.32 mg, 305.20 umol, 1.2 *eq*, HCl) was added. The mixture was stirred at 30 °C for 1.5 hr under N_2. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was added to H_2O (10 mL) and stirred for 10 min, then extracted with EtOAc (30 mL x 3). The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. Compound 4-chloro-N-(2,2-difluorospiro[2.5]octan-6-yl)-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide (5.3 mg, 15.57 umol, 6.12% yield, 99.833% purity) was obtained as a white solid.

LCMS (ESI) m/z 340.1 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d_4) = 8.72 (s, 1H), 8.13 (s, 1H), 7.31 (s, 1H), 4.05 - 3.94 (m, 1H), 2.03 (br d, J=9.0 Hz, 2H), 1.83 (br t, J=10.9 Hz, 2H), 1.69 - 1.45 (m, 4H), 1.17 - 1.08 (m, 2H).

Example 101. MPL-167

4-chloro-N- (4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



2 **MPL-167**

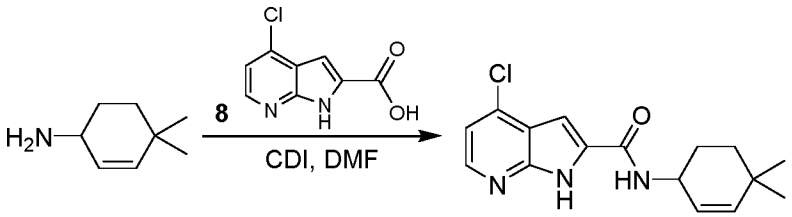
To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 508.67 umol, 1 *eq*) in DMF (1 mL) was added 1-methylimidazole (208.82 mg, 2.54 mmol, 202.74 uL, 5 *eq*). [chloro(dimethylamino)methylene]-dimethyl-ammonium;hexafluorophosphate (214.08 mg, 763.01 umol, 1.5 *eq*) and 4-fluoro-4-methyl-cyclohexanamine (110.86 mg, 661.27 umol, 1.3 *eq*, HCl). The mixture was stirred at 25 °C for 12 h. LCMS showed there were no starting material and main desired compound. The reaction mixture was added to water (15 mL), then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give crude product. The crude product was purified by prep-HPLC(column: YMC-Actus Triart C18 150*30 5u;mobile phase: [water(0.225%FA)-ACN];B%: 28%-55%,11min). The product 4-chloro-N- (4-fluoro-4-methyl-

cyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (20 mg, 64.11 umol, 12.60% yield, 99.3% purity) was obtained as white soild.

LCMS (ESI) m/z 310.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.61 (br s, 1H), 8.76 (s, 1H), 8.70 (d, *J*=8.2 Hz, 0.3H), 8.54 (d, *J*=7.6 Hz, 0.7H), 8.23 (s, 1H), 7.41 - 7.38 (m, 1H), 4.03 - 3.97 (m, 0.7H), 3.88 (br s, 0.3H), 1.89 - 1.83 (m, 3H), 1.77 - 1.63 (m, 3H), 1.63 - 1.54 (m, 2H), 1.42 (s, 1H), 1.38 (s, 1H), 1.35 (s, 0.5H), 1.30 (s, 0.5H).

Example 102. MPL-169

4-chloro-N-(4,4-dimethylcyclohex-2-en-1-yl)-1H-pyrrolo[2,3-c]pyridine -2-carboxamide



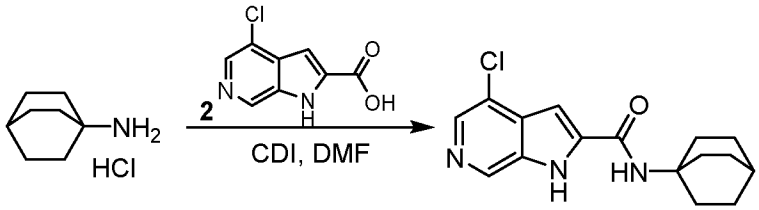
To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) in DMF (1 mL) was added CDI (82.48 mg, 508.67 umol, 2 *eq*) under N_2 atmosphere. The mixture was stirred at 30 °C for 0.5 hr under N_2 atmosphere. Then 4,4-dimethylcyclohex-2-en-1-amine (38.21 mg, 305.20 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 2 hr under N_2 atmosphere. LCMS showed there was no starting material and main desired compound. The mixture was added in water (10mL) and stirred for 10 mins. The mixture was extracted with EtOAc (15 mL x 3). The mixture was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by reversed-phase HPLC(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN];B%: 65%-83%,9min). Compound 4-chloro-N-(4,4-dimethylcyclohex-2-en-1-yl)- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide (10.6 mg, 34.54 umol, 13.58% yield, 99% purity) was obtained as a white solid.

LCMS (ESI) m/z 304.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d*6) δ =0.95 - 1.10 (m, 6 H) 1.23 (br s, 1 H) 1.42 - 1.53 (m, 1 H) 1.56 - 1.75 (m, 2 H) 1.86 (br d, *J*=3.91 Hz, 1 H) 4.49 (br d,

J=5.62 Hz, 1 H) 5.47 (dd, *J*=10.03, 2.45 Hz, 1 H) 5.55 - 5.61 (m, 1 H) 7.42 (s, 1 H) 8.18 (s, 1 H) 8.73 (s, 1 H) 8.78 (br d, *J*=8.07 Hz, 1 H) 12.49 (br s, 1 H).

Example 103. MPL-170

Synthesis of N-(4-bicyclo[2.2.2]octanyl)-4-chloro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



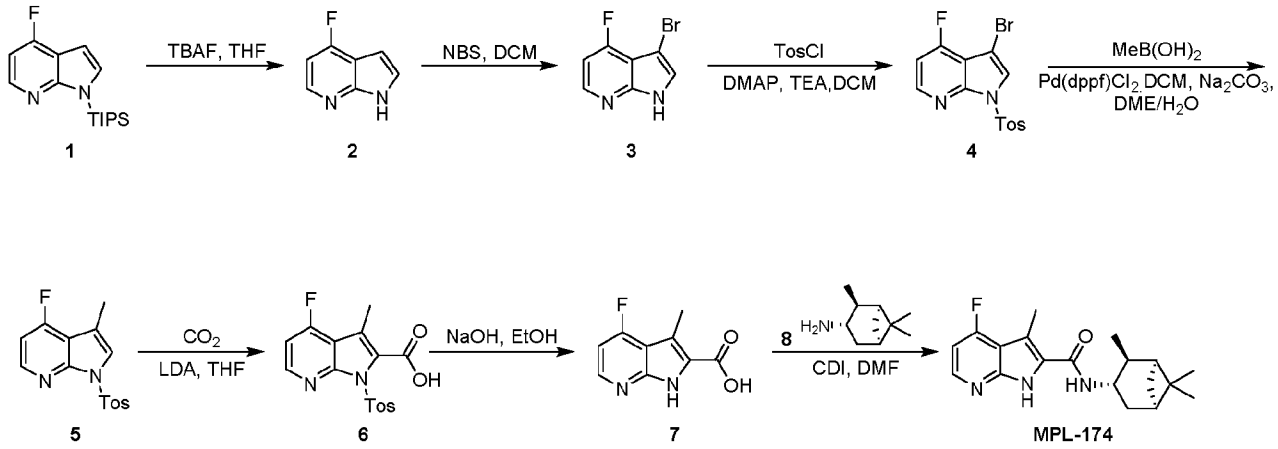
1 **MPL-170**

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) and bicyclo[2.2.2]octan-4-amine (61.68 mg, 381.50 umol, 1.5 *eq*, HCl) in DMF (1 mL) was added HOBt (51.55 mg, 381.50 umol, 1.5 *eq*) and EDCI (73.13 mg, 381.50 umol, 1.5 *eq*) TEA (77.21 mg, 763.01 umol, 106.20 uL, 3 *eq*), the mixture was stirred at 25 °C for 4 hr under N_2. LC-MS showed the starting material 1 was consumed completely and one main peak with desired mass was detected. The mixture was added to water (15mL) and stirred for 10min, filtered and the filter cake was dried under reduced pressure. The product N-(4-bicyclo[2.2.2]octanyl)-4-chloro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (54.9 mg, 179.67 umol, 70.64% yield, 99.417% purity) was obtained as white solid.

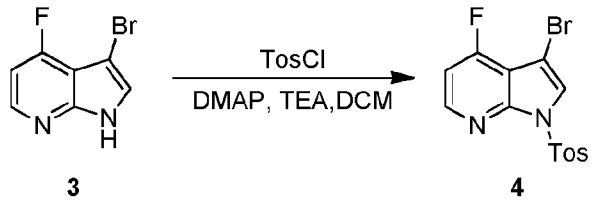
LCMS (ESI) m/z 304.0 $[M+H]^+$; ^1H NMR (500MHz, METHANOL-d4) = 12.34 (br s, 1H), 8.71 (s, 1H), 8.16 (s, 1H), 7.96 (s, 1H), 7.38 (s, 1H), 2.01 - 1.89 (m, 6H), 1.69 - 1.60 (m, 6H), 1.58 - 1.52 (m, 1H).

Example 104. MPL-174

Scheme

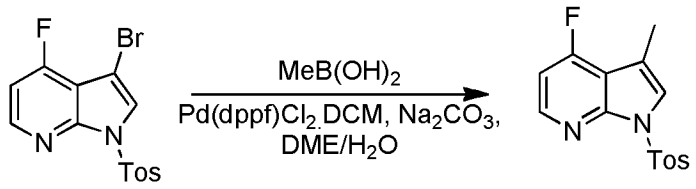


Synthesis of 3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 3-bromo-4-fluoro-1H-pyrrolo[2,3-b]pyridine (1.50 g, 6.98 mmol, 1 *eq*) and NaH (837.12 mg, 20.93 mmol, 60% purity, 3 *eq*) in THF (15 mL) at 0 °C was added TosCl (1.86 g, 9.77 mmol, 1.4 *eq*) the mixture was stirred at 25 °C for 12 h. TLC and LCMS showed the starting material 3 was consumed and the desired mass was detected. The reaction mixture was diluted with EtOAc (100 mL) and washed with brine(50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 3:1). The product 3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.8 g, 4.88 mmol, 69.89% yield) was obtained as brown solid.

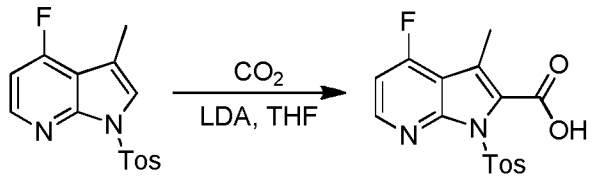
Synthesis of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid



4 5

To a solution of 3-bromo-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (400 mg, 1.08 mmol, 1 *eq*) and methylboronic acid (648.52 mg, 10.83 mmol, 10 *eq*) in DME (4.5 mL) and H2O (0.5 mL) was added Na_2CO_3 (344.49 mg, 3.25 mmol, 3 *eq*), $Pd(dppf)Cl_2.CH_2Cl_2$ (88.47 mg, 108.34 umol, 0.1 *eq*), methylboronic acid (648.52 mg, 10.83 mmol, 10 *eq*). The mixture was stirred at 80 °C for 12 hr under N_2. LCMS showed the completion of the reaction. The mixture was concentrated under reduce pressure to remove the DME, and diluted with water(100mL), then extracted with DCM(100 mL x 3). The combined organic layers dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Petroleum ether/EtOAc=1:0 to 1:1). The product 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.18 g, 1.55 mmol, 143.15% yield, 40% purity) was obtained as white solid.

Synthesis of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid

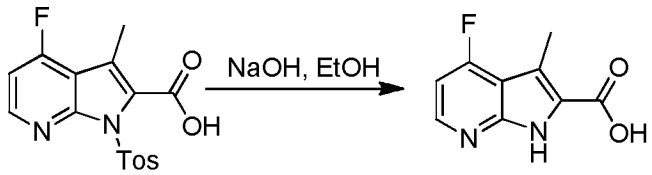


5 6

To a solution of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (480 mg, 1.58 mmol, 1 *eq*) in THF (6 mL) was added LDA (2 M, 1.18 mL, 1.5 *eq*) at -78°C under N_2, and the mixture was stirred at the same temperature for 1 h. Then CO_2 (69.41 mg, 1.58 mmol, 1 *eq*) was added and the mixture was stirred at the same temperature for 0.5 h. LCMS showed the desired product was detected. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) concentrated under reduced pressure to remove the THF. Then acidified with HCl (2 M) to pH =

5. The mixture was filtered and the filter cake was washed with 30 mL x 3 of Petroleum ether, dried under reduced pressure to give the product. The product 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine-2-carboxylic acid (500 mg, 1.44 mmol, 91.01% yield) was obtained as white solid.

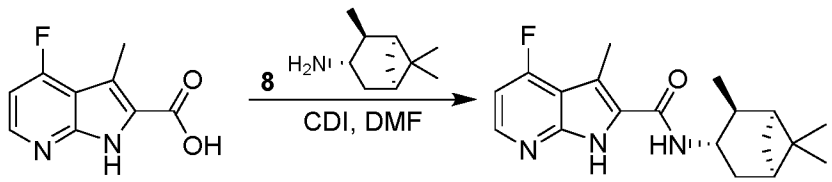
Synthesis of 4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



6 **7**

To a solution of 4-fluoro-3-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (500 mg, 1.44 mmol, 1 *eq*) in THF (3 mL) was added NaOH (2 M, 2.18 mL, 3.04 *eq*), the mixture was stirred at 75 °C for 2 h. LCMS showed the desired product was detected. The reaction was concentrated under reduced pressure to remove the THF, then acidified with HCl (2 M) to pH = 5. The mixture was filtered and the filter cake was washed with 30 mL x 3 of Petroleum ether, dried under reduced pressure to give the product. After concentration, the crude product was used directly for the next step without purification. The product 4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (220 mg, 453.23 umol, 31.58% yield, 40% purity) was obtained as brown solid.

Synthesis of 4-fluoro-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl] -1H-pyrrolo[2,3-b]pyridine-2-carboxamide



7 **MPL-174**

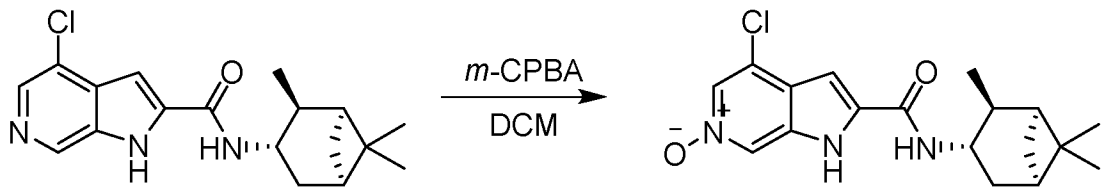
To a solution of 4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (220 mg, 1.13 mmol, 1 *eq*) in DMF (3 mL) was added CDI (275.59 mg, 1.70 mmol, 1.5 *eq*). The mixture was stirred at 25°Cfor 0.5h, then (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (260.49 mg, 1.70

mmol, 1.5 *eq*) was added and the mixture was stirred for 0.5 h at the same temperature. LCMS showed the reactant 7 was consumed and the desired mass was detected. The residue was purified by Prep—HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 65%-88%,11min) without the further workup. The product 4-fluoro-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (37.6 mg, 113.48 umol, 10.02% yield, 99.417% purity) was obtained as white solid.

LCMS (ESI) m/z 330.2 $[M+H]^+$; ^1H NMR (400MHz, CHLOROFORM-d) = 9.94 (br s, 1H), 8.37 (dd, *J*=5.4, 7.7 Hz, 1H), 6.80 (dd, *J*=5.4, 10.6 Hz, 1H), 5.95 (br d, *J*=8.7 Hz, 1H), 4.59 - 4.45 (m, 1H), 2.82 - 2.74 (m, 1H), 2.72 (s, 3H), 2.54 - 2.47 (m, 1H), 2.09 - 2.01 (m, 1H), 1.98 - 1.90 (m, 2H), 1.69 (ddd, *J*=2.4, 6.0, 14.2 Hz, 1H), 1.28 (s, 3H), 1.23 (d, *J*=7.2 Hz, 3H), 1.11 (s, 3H), 0.94 (d, *J*=9.9 Hz, 1H).

Example 105. MPL-187

Synthesis of 4-chloro-6-oxido-N-[(1S,2S,3S,5R)-2,6,6- trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-c]pyridin-6-ium-2-carboxamide



3 **MPL-187**

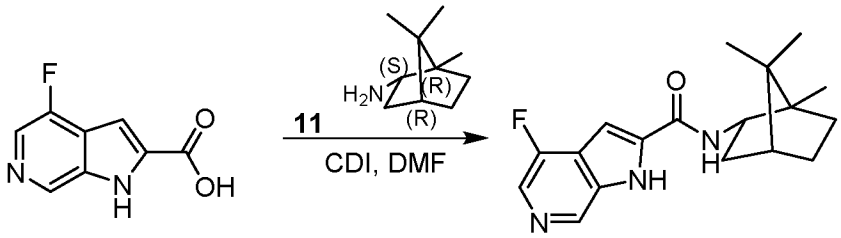
To a solution of 4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine -2-carboxamide (90 mg, 271.22 umol, 1 *eq*) and *m*-CPBA (175.51 mg, 813.65 umol, 80% purity, 3 *eq*) in DCM (3 mL). The mixture was stirred at 30 °C for 24 hr. LCMS showed most the starting material was consumed. The mixture was diluted with Na_2SO_3 (10 mL). It was extracted with DCM : MeOH (15mL x 3, 10:1). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM : MeOH=10:1). The product 4-chloro-6-oxido-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridin-6-ium-2-carboxamide (10.4 mg, 29.90 umol,

11.02% yield, 100% purity) was obtained as white solid. Purity comes from LCMS and the product was confirmed by ^{1}H NMR.

LCMS (ESI) m/z 348.1 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d6) δ = 12.23 (br s, 1H), 8.63 (br d, *J*=8.3 Hz, 1H), 8.32 (s, 1H), 8.17 (d, *J*=1.5 Hz, 1H), 7.39 (s, 1H), 4.37 (quin, *J*=8.0 Hz, 1H), 2.44 (br s, 1H), 2.38 (br d, *J*=6.8 Hz, 1H), 2.36 - 2.36 (m, 1H), 2.07 (br t, *J*=7.2 Hz, 1H), 1.95 (br s, 1H), 1.82 (br t, *J*=5.4 Hz, 1H), 1.69 (br dd, *J*=6.4, 11.7 Hz,1H), 1.23 (s, 4H), 1.19 (d, *J*=9.5 Hz, 1H), 1.08 - 1.04 (m, 6H).

Example 106. MPL-188

4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



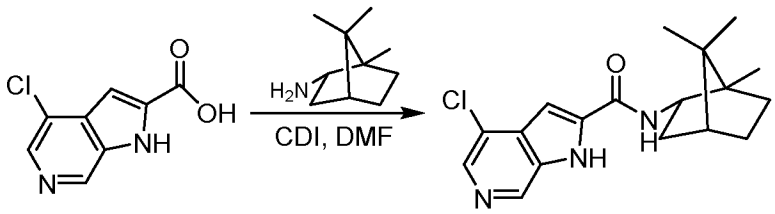
10 **MPL-188**

To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 222.05 umol, 1 *eq*) in DMF (1 mL) was added CDI (43.21 mg, 266.47 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5h. 1,7,7-trimethylnorbornan-2-amine (40.84 mg, 266.47 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed the starting material 1 was consumed completely. The reaction mixture was added to water (20ml), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The product 4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (19.9 mg, 63.10 umol, 28.42% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 316.1 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d6) δ = 8.65 (d, *J*=2.7 Hz, 1H), 8.33 (d, *J*=8.4 Hz, 1H), 8.09 (d, *J*=2.0 Hz, 1H), 7.51 (s, 1H), 4.43 - 4.37 (m, 1H), 2.23 - 2.16 (m, 1H), 1.78 (ddd, *J*=4.2, 9.2, 13.0 Hz, 1H), 1.71 - 1.64 (m, 2H), 1.45 - 1.38 (m, 1H), 1.26 (br t, *J*=12.7 Hz, 1H), 1.17 (dd, *J*=4.9, 13.0 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

Example 107. MPL-189

Synthesis of 4-chloro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-Carboxamide



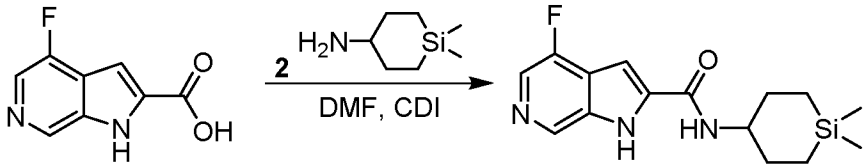
1 **MPL-189**

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (150 mg, 763.01 umol, 1 *eq*) and CDI (148.46 mg, 915.61 umol, 1.2 *eq*) in DMF (5 mL). The mixture was stirred at 25 °C for 0.5 h. 1,7,7-trimethylnorbornan-2-amine (140.33 mg, 915.61 umol, 1.2 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. LCMS showed no starting material. The reaction mixture was added to water (20 ml), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL) and then lyophilized. The product 4-chloro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide (196.1 mg, 590.95 umol, 77.45% yield, 100% purity) was obtained as white solid.

LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d6*) δ = 12.44 (br s, 1H), 8.73 (s, 1H), 8.42 (br d, *J*=8.5 Hz, 1H), 8.19 (s, 1H), 7.51 (s, 1H), 4.45 - 4.37 (m, 1H), 2.24 - 2.15 (m, 1H), 1.78 (ddd, *J*=4.1, 9.1, 13.0 Hz, 1H), 1.74 - 1.65 (m, 2H), 1.43 (dt, *J*=4.0, 10.3 Hz, 1H), 1.27 (br t, *J*=11.6 Hz, 1H), 1.19 (dd, *J*=5.0, 12.9 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

Example 108. MPL-191

N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



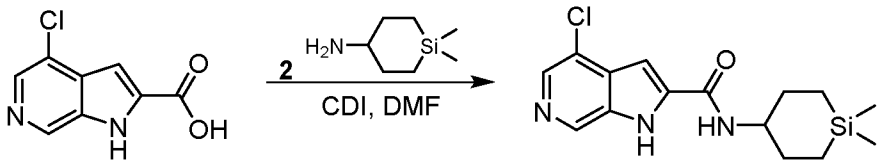
1 MPL-191

To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (200 mg, 1.11 mmol, 1 *eq*) and CDI (216.04 mg, 1.33 mmol, 1.2 *eq*) in DMF (2 mL). The mixture was stirred at 25 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (190.93 mg, 1.33 mmol, 1.2 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. LCMS showed no starting material. The reaction mixture was added to water (20 mL). Then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The crude product was purified by re-crystallization from EtOAc (20 mL) at 100 °C to give crude product. The desired product was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 42%-70%,11min). The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized to give p2. The product N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (54.9 mg, 177.06 umol, 15.95% yield, 98.5% purity) was obtained as white solid. The product 2 N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (40 mg, 121.80 umol, 10.97% yield, 93.0% purity) was obtained as white solid.

LCMS (ESI) m/z 306.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.43 (br s, 1H), 8.64 (d, *J*=2.4 Hz, 1H), 8.53 (br d, *J*=8.1 Hz, 1H), 8.08 (d, *J*=1.5 Hz, 1H), 7.32 (s, 1H), 3.74 (dt, *J*=8.5, 11.1 Hz, 1H), 2.01 (br d, *J*=9.5 Hz, 2H), 1.66 - 1.54 (m, 2H), 0.78 (br d, *J*=14.5 Hz, 2H), 0.62 (dt, *J*=4.7, 14.1 Hz, 2H), 0.09 (s, 3H), 0.04 (s, 3H).

Example 109. MPL-192

Synthesis of 4-chloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide



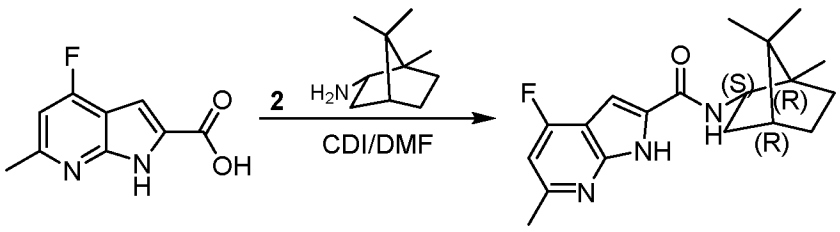
1 MPL-192

To a solution of 4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (150 mg, 763.01 umol, 1 *eq*) in DMF (4 mL) was added CDI (160.84 mg, 991.91 umol, 1.3 *eq*). The mixture was stirred at 25 °C for 0.5 h. Then 1,1-dimethylsilinan-4-amine (142.14 mg, 991.91 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there was no starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc (30 mL), dried with anhydrous $MgSO_4$, filtered. The filtrate was concentrated in vacuo. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL) lyophilized without further purification. Compound 4-chloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (116.2 mg, 342.06 umol, 44.83% yield, 94.75% purity) was obtained as a white solid.

LCMS (ESI), m/z 322.1[M+H]$^+$; ^{1}H NMR (500MHz, CHLOROFORM-d) δ= 10.78 (br s, 1H), 8.85 (s, 1H), 8.32 - 8.28 (m, 1H), 6.93 (d, *J*=1.5 Hz, 1H), 6.28 (br d, *J*=7.9 Hz, 1H), 4.04 - 3.95 (m, 1H), 2.28 - 2.21 (m, 2H), 1.70 - 1.63 (m, 2H), 1.29 - 1.25 (m, 1H), 0.89 - 0.71 (m, 4H), 0.10 (d, *J*=16.5 Hz, 6H).

Example 110. MPL-194

Synthesis of 4-fluoro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



1 **MPL-194**

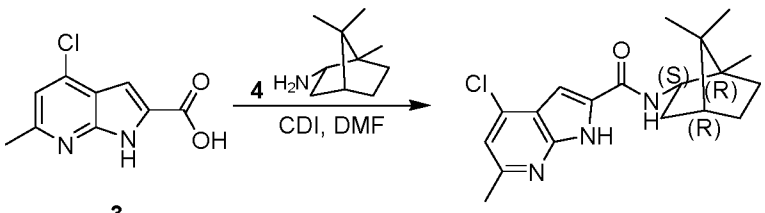
To a solution of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 515.03 umol, 1 *eq*) in DMF (0.5 mL) was added CDI (108.57 mg, 669.54 umol, 1.3 *eq*). The mixture was stirred at 15 °C for 0.5 h. 1,7,7-trimethylnorbornan-2-amine (102.62 mg, 669.54 umol, 1.3 *eq*) was added and the mixture was stirred at 15 °C for 1.5 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in

CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was purified by column chromatography (SiO_2, Petroleum ether:EtOAc = 3:1 to 2:1). From LCMS, the product was diluted in CH_3CN (5 mL) and in ultrasound wave for 2 h. There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. 4-fluoro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (100 mg, 303.57 umol, 1 *eq*) was diluted in CH_3CN(10 mL) and in ultrasound wave for 2 h. There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. Compound 4-fluoro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)- 1H-pyrrolo[2,3-b]pyridine-2-carboxamide (65 mg, 196.34 umol, 64.68% yield, 99.50% purity) was obtained as a white solid.

LCMS (ESI) m/z 330.1 $[M+H]^+$; ^1H NMR (500MHz, CHLOROFORM-d) 9.57 (br s, 1H), 6.84 (s, 1H), 6.72 (d, *J*=10.5 Hz, 1H), 6.16 (br d, *J*=8.5 Hz, 1H), 4.49 - 4.42 (m, 1H), 2.64 - 2.61(m, 3H), 2.50 - 2.42 (m, 1H), 1.84 (tdd, *J*=3.9, 8.4, 16.4 Hz, 1H), 1.74 (t, *J*=4.5 Hz, 1H), 1.58 (ddd, *J*=4.4, 9.4, 13.9 Hz, 2H), 1.52 - 1.45 (m, 1H), 1.30 - 1.23(m, 1H), 1.00 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H).

Example 111. MPL-195

Synthesis of 4-chloro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



3 **MPL-195**

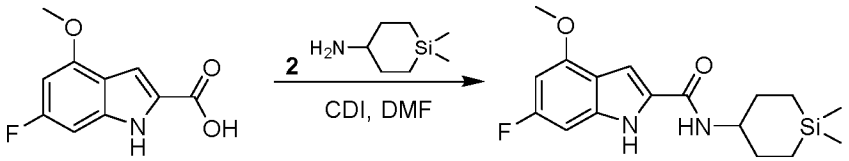
To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (0.3 g, 1.42 mmol, 1 *eq*) in DMF (5 mL) (dried by CaH_2) was added CDI (277.16 mg, 1.71 mmol, 1.2 *eq*). The mixture was stirred at 15 °C for 0.5 h. Then 1,7,7-trimethylnorbornan-2-amine (261.97 mg, 1.71 mmol, 1.2 *eq*) was added, the mixture was stirred further 12 hr at 30 °C. LCMS showed Reactant 3 was consumed completely and one main peak with desired mass was detected. The

reaction mixture was dropped into water (30mL); the product was isolated as white solid. Filtered, the filter cake was washed with water (10 mL x 2) to afford the product which was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/Petroleum ether gradient at 18/min). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 2 :1, Rf = 0.5) was combined and concentrated under reduced pressure to give 4-chloro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide (297 mg, 854.35 umol, 59.98% yield, 99.492% purity) was obtained as a light yellow solid.

LCMS (ESI) m/z 346.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.29 (s, 1 H), 8.14 (d, *J*=8.61 Hz, 1 H), 7.32 (d, *J*=2.35 Hz, 1 H), 7.16 (s, 1 H), 4.37 (br s, 1 H), 2.51 - 2.54 (m, 3 H), 2.18 (br t, *J*=11.74 Hz, 1 H), 1.72 - 1.83 (m, 1 H), 1.62 - 1.72 (m, 2 H), 1.37 - 1.45 (m, 1 H), 1.21 - 1.29 (m, 1 H), 1.14 (dd, *J*=12.72, 4.89 Hz, 1 H), 0.95 (s, 3 H), 0.85(s, 3 H), 0.76 (s, 3 H).

Example 112. MPL-196

N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-indole-2-carboxamide

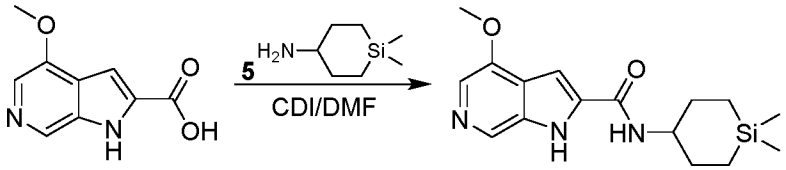


To a solution of 6-fluoro-4-methoxy-1H-indole-2-carboxylic acid (160 mg, 764.91 umol, 1 *eq*) and CDI (148.84 mg, 917.90 umol, 1.2 *eq*) in DMF (2 mL). The mixture was stirred at 25 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (131.54 mg, 917.90 umol, 1.2 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. LCMS showed no starting material. TLC showed one spot was observed. The reaction mixture was added to water (20 ml), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 10:1). The residue was diluted in CH_3CN (5 mL) and H2O (20 mL), then lyophilized. The product N-(1,1-dimethylsilinan-4-yl)-6- fluoro-4-methoxy-1H-indole-2-carboxamide (141.9 mg, 421.30 umol, 55.08% yield, 99.3% purity) was obtained as white solid.

LCMS (ESI) m/z 335.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d6*) δ = 11.57 (s, 1H), 8.13 (d, *J*=8.1 Hz, 1H), 7.22 (d, *J*=1.7 Hz, 1H), 6.71 (dd, *J*=1.3, 9.5 Hz, 1H), 6.45 (dd, *J*=1.8, 12.1 Hz, 1H), 3.88 (s, 3H), 3.75 - 3.64 (m, 1H), 2.00 - 1.92 (m, 2H), 1.62 - 1.52 (m, 2H), 0.76 (br d, *J*=14.5 Hz, 2H), 0.59 (dt, *J*=4.7, 14.2 Hz, 2H), 0.08 (s, 3H), 0.03 (s, 3H).

Example 113. MPL-202

N-(1,1-dimethylsilinan-4-yl)-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



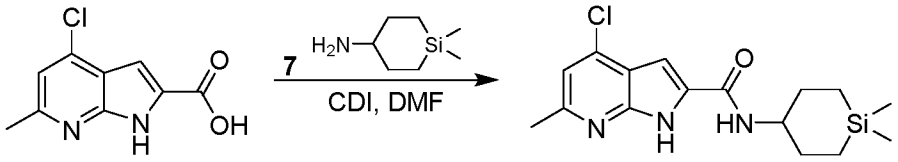
4 **MPL-202**

To a solution of 4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (200 mg, 1.04 mmol, 1 *eq*) and CDI (202.51 mg, 1.25 mmol, 1.2 *eq*) in DMF (2 mL). The mixture was stirred at 25 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (178.97 mg, 1.25 mmol, 1.2 *eq*) was added. The mixture was stirred at 25 °C for 11.5 h. LCMS showed no starting material. The reaction mixture was added to water (20 mL). Then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product N-(1,1-dimethylsilinan-4-yl)-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (137.3 mg, 407.41 umol, 39.15% yield, 94.2% purity) was obtained as yellow solid.

LCMS (ESI) m/z 318.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d6*) δ = 12.02 (br s, 1H), 8.43 (s, 1H), 8.37 (d, *J*=8.2 Hz, 1H), 7.79 (s, 1H), 7.28 (s, 1H), 3.97 (s, 3H), 3.77 - 3.67 (m, 1H), 2.05 - 1.95 (m, 2H), 1.66 - 1.54 (m, 2H), 0.77 (br d, *J*=14.5 Hz, 2H), 0.61 (dt, *J*=4.6, 14.1 Hz, 2H), 0.09 (s, 3H), 0.03 (s, 3H).

Example 116. MPL-208

Synthesis of 4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine- 2-carboxamide



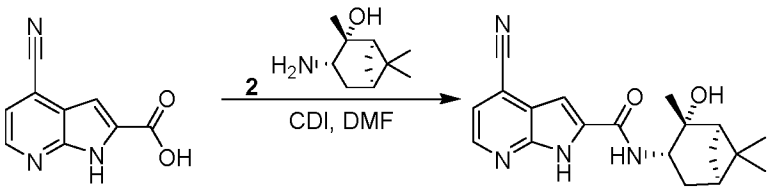
6 MPL-208

To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (330 mg, 1.57 mmol, 1 *eq*) in DMF (5 mL) was added CDI (330.28 mg, 2.04 mmol, 1.3 *eq*). The mixture was stirred at 10 °C for 0.5 hr. Then 1,1-dimethylsilinan-4-amine (291.89 mg, 2.04 mmol, 1.3 *eq*) was added. The mixture was stirred at 30 °C further 1 hr. LCMS showed Reactant 1 was consumed completely and one main peak with desired mass was detected. The reaction mixture was dropped into water (50 mL), filtered to afford the crude product which was redissovled in DMF (5 mL), filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.05%HCl)-ACN];B%: 53%-83%,10min). Compound 4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (110 mg, 327.48 umol, 20.90% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 336.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.20 (br s, 1 H), 8.26 (d, *J*=8.09 Hz, 1 H), 7.10 (d, *J*=1.98 Hz, 1 H), 7.08 (s, 1 H), 3.61 (td, *J*=11.22, 8.09 Hz, 1 H), 2.44 (s, 3 H), 1.84 - 1.94 (m, 2 H), 1.45 - 1.56 (m, 2 H), 0.69 (br d, *J*=14.50 Hz, 2 H), 0.52 (td, *J*=14.08, 4.81 Hz, 2 H), 0.00 (s, 3 H) -0.05 (s, 3 H).

Example 117. MPL-215

Synthesis of 4-cyano-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3 -yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



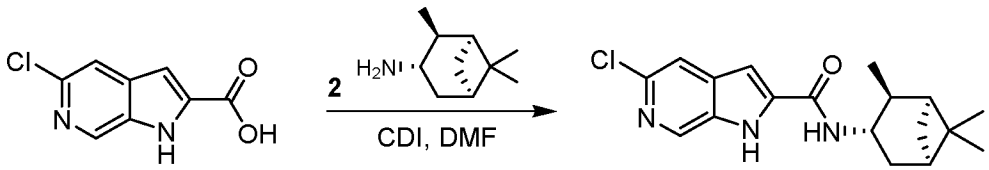
1 MPL-215

To a solution of 4-cyano-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 534.32 umol, 1 *eq*) and CDI (112.63 mg, 694.61 umol, 1.3 *eq*) in DMF (1.5 mL). The mixture was stirred at 30°C for 0.5 h. Then (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (117.57 mg, 694.61 umol, 1.3 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LC-MS showed most of the starting material was consumed. The reaction mixture was added to water (20 mL), then filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The residue was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product 4-cyano-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (58.3 mg, 159.32 umol, 29.82% yield, 92.478% purity) was obtained as a white solid.

LCMS (ESI) m/z 321.2 $[M\text{-}OH^-]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.89 (br s, 1H), 8.54 - 8.50 (m, 1H), 8.23 (br d, J=9.0 Hz, 1H), 7.64 (d, J=4.9 Hz, 1H), 7.49 (s, 1H), 4.62 - 4.49 (m, 2H), 2.27 (br t, J=11.1 Hz, 1H), 2.17 - 2.09 (m, 1H), 1.90 (br d, J=5.6 Hz, 2H), 1.75 - 1.61 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H), 1.07 (s, 3H).

Example 118. MPL-126

Synthesis of 5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



1 **MPL-126**

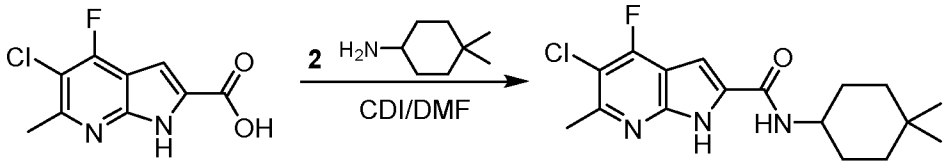
To a solution of 5-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (80 mg, 406.94 umol, 1 *eq*) in DMF (2.0 mL) was added CDI (92.38 mg, 569.71 umol, 1.4 *eq*) and stirred at 30 °C for 1 h. Then, (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (106.03 mg, 691.79 umol, 1.7 *eq*) was added above solution and stirred at 30 °C for 2 h. LCMS showed the starting material was consumed completely and the desired mass was detected. The mixture was added water (10 mL) and extracted with EtOAc (15 mL x 3). The organic phase was washed with water (10 mL x 3) and brine (10 mL x 3), dried over Na_2SO_4 and filtered and concentrated under reduced pressure

to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 200:1). Compound 5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (62.4 mg, 187.50 umol, 46.08% yield, 99.7% purity) was obtained as a white solid.

LCMS (ESI) m/z 332.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.26 (s, 1H), 8.67 (br d, *J*=8.4 Hz, 1H), 8.58 (s, 1H), 7.78 (s, 1H), 7.25 (s, 1H), 4.40 (td, *J*=7.9, 16.4 Hz, 1H), 2.47 - 2.34 (m, 2H), 2.10 (quin, *J*=6.9 Hz, 1H), 1.96 (br s, 1H), 1.82 (br t, *J*=5.6 Hz, 1H), 1.72 (br dd, *J*=6.4, 12.2 Hz, 1H), 1.26 - 1.19 (m, 4H), 1.10 - 1.03 (m, 6H).

Example 119. MPL-069

Synthesis of 5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



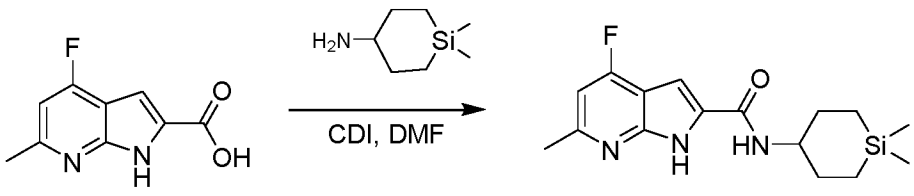
1 **MPL-069**

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (80 mg, 349.95 umol, 1 *eq*) in DMF (1 mL) was added CDI (85.12 mg, 524.92 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 0.5 h. Then 4,4-dimethylcyclohexanamine (66.78 mg, 524.92 umol, 1.5 *eq*) was added , the mixture was stirred at 25 °C for 0.5 h. LCMS showed the reaction was consumed and the desired mass was detected. The mixture was purified by prep-HPLC without work up. The residue was purified by prep-HPLC (column: Boston Green ODS 150*30 5u; mobile phase. [water(0.225%FA)-ACN];B%: 65%-85%,10min) to give the white solid(25mg) and the further purification by SFC (column: DAICEL CHIRALCEL OD-H(250mm*30mm,5um);mobile phase: [0.1%NH3H2O ETOH];B%: 25%-25%,min) (SFC (t=7.717min). The product 5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2- carboxamide (12.5 mg, 36.95 umol, 10.56% yield, 99.854% purity) was obtained as white solid.

LCMS (ESI) m/z 334.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.50 (br s, 1H), 8.32 (d, *J*=8.2 Hz, 1H), 7.22 (s, 1H), 3.79 - 3.66 (m, 1H), 2.62 (s, 3H), 1.67 (br dd, *J*=3.5, 12.9 Hz, 2H), 1.58 - 1.46 (m, 2H), 1.44 - 1.37 (m, 2H), 1.31 - 1.23 (m, 2H), 0.93 (d, *J*=7.8 Hz, 6H).

Example 120. MPL-207

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

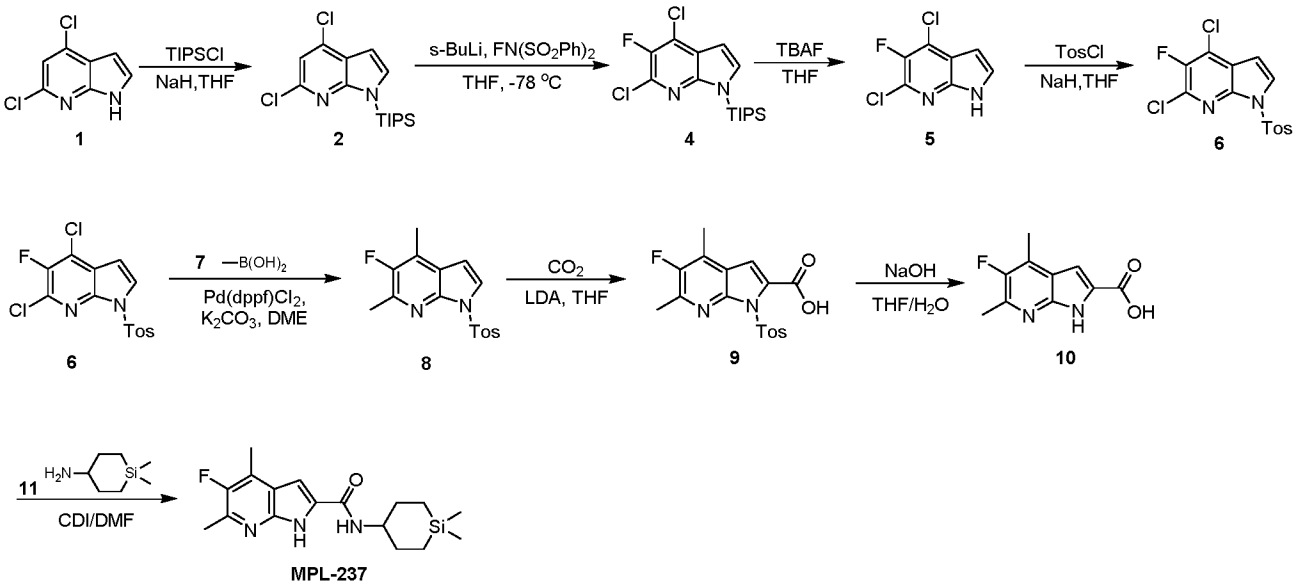


To a solution of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (150 mg, 772.55 umol, 1 *eq*) in DMF (0.5 mL) was added CDI (150.32 mg, 927.06 umol, 1.2 *eq*). The mixture was stirred at 15 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (132.85 mg, 927.06 umol, 1.2 *eq*) was added and the mixture was stirred at 15 °C for 1.5 h. LCMS showed there were no starting material and main desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by silica column chromatography (eluent of 0~50% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain product by TLC (Petroleum ether:EtOAc = 2:1, Rf = 0.3) were combined and evaporated. Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carbox amide (110 mg, 341.52 umol, 44.21% yield, 99.18% purity) was obtained as a white solid which was confirmed by LCMS and ^1H NMR.

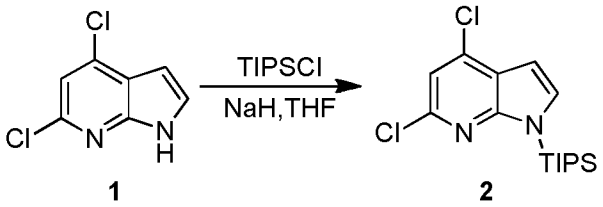
LCMS (ESI) m/z 320.1 $[M+H]^+$; ^1H NMR (400MHz, CHLOROFORM-d) = 9.82 (br s, 1H), 6.74 (s, 1H), 6.67 (d, *J*=10.5 Hz, 1H), 6.03 (br d, *J*=8.1 Hz, 1H), 3.91 - 3.81 (m, 1H), 2.59 (s, 3H), 2.13 (td, *J*=3.3, 9.2 Hz, 2H), 1.60 - 1.46 (m, 2H), 0.79 - 0.61 (m, 4H), 0.04 (s, 3H), 0.00 (s, 3H).

Example 121. MPL-237

Scheme

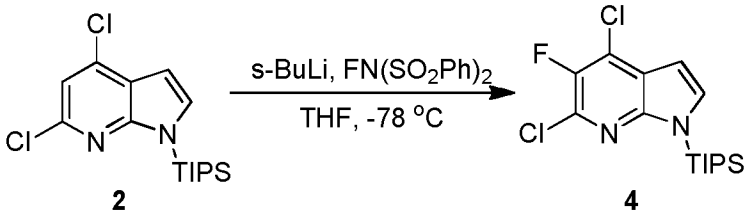


Synthesis of (4, 6-dichloropyrrolo[2, 3-b]pyridin-1-yl)-triisopropyl-silane



To a solution of NaH (522.92 mg, 13.07 mmol, 60% purity, 3 *eq*) in 5 mL THF was added a solution of 4,6-dichloro-1H-pyrrolo[2,3-b]pyridine (0.815 g, 4.36 mmol, 1 *eq*) in 10 mL THF at 0 °C under N_2, then TIPSCl (1.26 g, 6.54 mmol, 1.40 mL, 1.5 *eq*) was added at 0 °C under N_2. The mixture was stirred at 10 °C for 12 hrs under N_2 atmosphere. TLC (Petroleum ether: EtOAc=1:0) showed there was no starting material. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (10 mL) 0 °C, and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether ： EtOAc = 1:0). The product (4, 6-dichloropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (1.17 g, 3.25 mmol, 74.54% yield, 95% purity) was obtained as white oil.

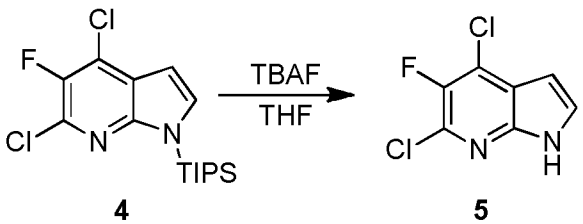
Synthesis of (4,6-dichloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



2 **4**

To a solution of (4,6-dichloropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (1.1 g, 3.20 mmol, 1 *eq*) in THF (10 mL) at -78 °C under N_2 was treated dropwise with s-BuLi (1.3 M, 5.42 mL, 2.2 *eq*). The reaction was then stirred for 30 minutes. Then NFSI (2.53 g, 8.01 mmol, 2.5 *eq*) in THF (20 mL) was added dropwise. The mixture was stirred for 11.5 h at 10 °C under N_2. LCMS showed there was no starting material. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (20 mL). The aqueous phase was extracted with EtOAc (50 mL x 3). The combined hexane phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether：EtOAc = 1:0). (4,6-Dichloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (0.942 g, 2.22 mmol, 69.17% yield, 85% purity) was obtained as a white solid.

Synthesis of 4, 6-dichloro-5-fluoro-1H-pyrrolo[2,3-b]pyridine



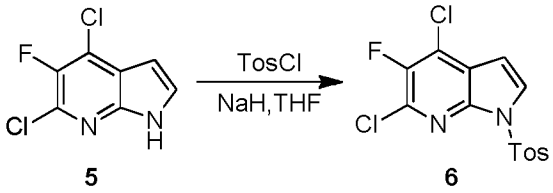
4 **5**

To a solution of (4,6-dichloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (0.942 g, 2.61 mmol, 1 *eq*) in THF (5 mL) was added TBAF (1 M, 3.91 mL, 1.5 *eq*). The mixture was stirred at 10 °C for 12 hr. TLC (Plate 1: Petroleum ether: EtOAc=1:0) showed there was no starting material. The mixture was concentrated in reduced pressure until without THF. The residue was washed with saturated brine (50 mL). The aqueous phase was extracted with EtOAc (50 mL x 3), dried with anhydrous Na_2SO_4, filtered. The filtrate was concentrated in vacuo. The

residue was purified by column chromatography (SiO_2, Petroleum ether ： EtOAc = 1:0 to 3:1).

Compound 4,6-dichloro-5-fluoro-1H-pyrrolo[2,3-b]pyridine (629 mg, 2.45 mmol, 94.15% yield, 80% purity) was obtained as a white solid.

Synthesis of 4,6-dichloro-5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

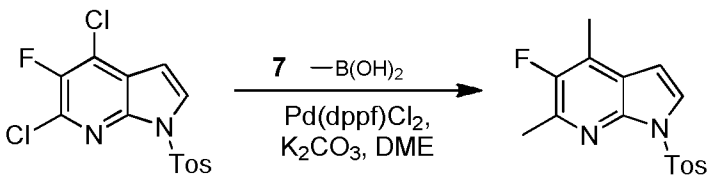


5 **6**

To a solution of 4,6-dichloro-5-fluoro-1H-pyrrolo[2,3-b]pyridine (487 mg, 2.38 mmol, 1 *eq*) in THF (10 mL) was added NaH (285.05 mg, 7.13 mmol, 60% purity, 3 *eq*) and 4-methylbenzenesulfonyl chloride (905.74 mg, 4.75 mmol, 2 *eq*) at 0 °C under N_2. The mixture was stirred at 10 °C for 12 h.

TLC (Petroleum ether: EtOAc=5:1, R_f=0.6) showed there was no starting material and main desired compound. The reaction was added dropwise in saturated aqueous NH_4Cl (10 mL) at 0°C. The aqueous phase was adjusted pH=7 with HCl (2 M). The mixture was concentrated under pressure until without THF. The residue was extracted with EtOAc (10 mL x 3). The combined hexane phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1 : 0 to 10 : 1). The compound 4,6-dichloro-5-fluoro-1-(p-tolylsulfonyl) pyrrolo[2,3-b] pyridine (802 mg, 1.79 mmol, 75.19% yield, 80% purity) was obtained as a white solid.

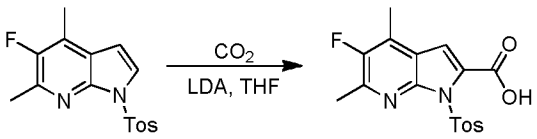
Synthesis of 5-fluoro-4,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



6 **8**

To a solution of 4,6-dichloro-5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1 g, 2.23 mmol, 1 *eq*), methylboronic acid (1.33 g, 22.27 mmol, 10 *eq*) and K_2CO_3 (923.45 mg, 6.68 mmol, 3 *eq*) in DME (10 mL) was degassed with N_2 for 3 times. Then $Pd(dppf)Cl_2$ (162.96 mg, 222.72 umol, 0.1 *eq*) was added, the mixture was degassed with N_2 for 3 times and stirred at 110 °C for 12 hr under N_2. LCMS showed there was no starting material and main desired compound. The reaction mixture was concentrated under reduced pressure to give a residue. There residue was diluted with EtOAc (50 mL). The mixture was washed with NaCl (50 x 2 mL). The combine phase was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1 : 0 to 1 : 1). The compound 5-fluoro-4, 6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (406 mg, 1.21 mmol, 54.40% yield, 95% purity) was obtained as a white solid. The compound 5-fluoro-4, 6-dimethyl-1-(p-tolylsulfonyl) pyrrolo[2,3-b]pyridine (436 mg, 1.23 mmol, 55.34% yield, 90% purity) was obtained as white solid.

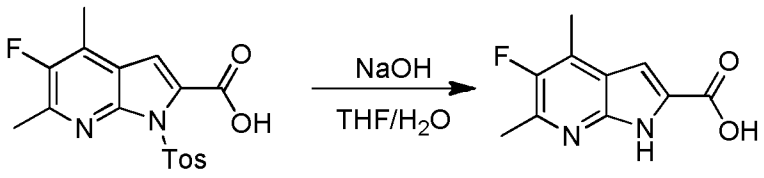
Synthesis of 5-fluoro-4, 6-dimethyl-1-(p-tolylsulfonyl) pyrrolo [2, 3-b] pyridine-2- carboxylic acid



8 **9**

To a solution of 5-fluoro-4,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (231 mg, 725.58 umol, 1 *eq*) in THF(5 mL) at -78 °C under N_2 was treated dropwise with LDA (2 M, 689.30 uL, 1.9 *eq*). The reaction was stirred for 1.5 h. The mixture was stirred for 10.5 h at 10 °C under CO_2 (15 Psi). LCMS showed there were main desired compound and a little starting material (2%). The residue was used directly for next step without further work up. The residue was used directly for next step without further purification. The product 5-fluoro-4,6-dimethyl-1-(p-tolylsulfonyl) pyrrolo[2,3-b]pyridine-2-carboxylic acid (262.93 mg, crude) was obtained as a white solid. LCMS (ESI), m/z 363.1$[M+H]^+$.

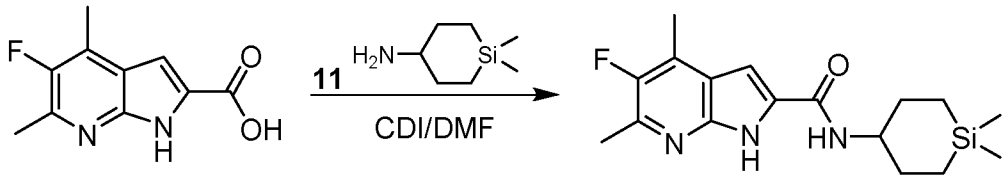
Synthesis of 5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



9 10

To a solution of 5-fluoro-4, 6-dimethyl-1-(p-tolylsulfonyl) pyrrolo [2, 3-b]pyridine-2-carboxylic acid (262.93 mg, 725.57 umol, 1 *eq*). The mixture was dropwise added NaOH (4 M, 8 mL, 44.10 *eq*) until pH=12. The reaction was stirred at 30 °C-70 °C for 2 hr. LCMS showed there was main starting material. The mixture was stirred at 70 °C for 12 hr. LCMS showed there was no starting material and main desired compound. The mixture was concentrated in reduced pressure until without THF. The residue adjusted to pH 4 with HCl (2N), filtered. The cake was transferred the bottom flask. The residue was used directly for next step without further purification. Compound 5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (109 mg, 471.21 umol, 64.94% yield, 90% purity) was obtained as a white solid.

Synthesis of N-(1,1-dimethylsilinan-4-yl)-5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



10 MPL-237

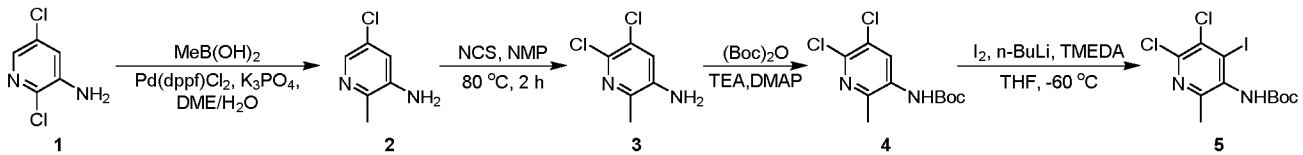
To a solution of 5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (109 mg, 523.56 umol, 1 *eq*) in DMF (1 mL) was added CDI (110.36 mg, 680.63 umol, 1.3 *eq*). The mixture was stirred at 30 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (97.54 mg, 680.63 umol, 1.3 *eq*) was added and the mixture was stirred at 30 °C for 2 h. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by preparative HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 60%-85%,11min). Compound N-(1,1-dimethylsilinan-4-yl)-5-fluoro-4,6-dimethyl-

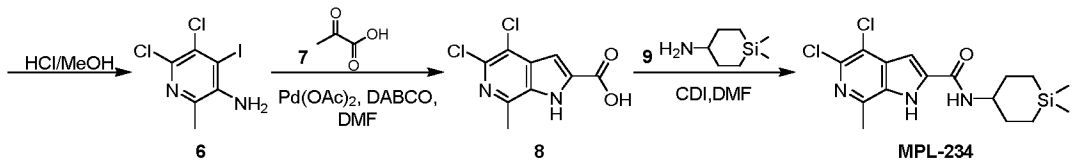
1H-pyrrolo[2,3-b]pyridine-2-carboxamide (37.4 mg, 110.07 umol, 21.02% yield, 98.14% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR.

LCMS (ESI), m/z 334.1[M+H]$^+$; ^{1}H NMR (400MHz, METHANOL-d_4) δ= 7.13 (s, 1H), 3.78 (br t, J=11.0 Hz, 1H), 2.52 (d, J=3.5 Hz, 3H), 2.49 (d, J=2.0 Hz, 3H), 2.13 (br d, J=9.4 Hz, 2H),1.71 - 1.60 (m, 2H), 0.87 - 0.80 (m, 2H), 0.75 - 0.66 (m, 2H), 0.12 (s, 3H), 0.05 (s, 3H).

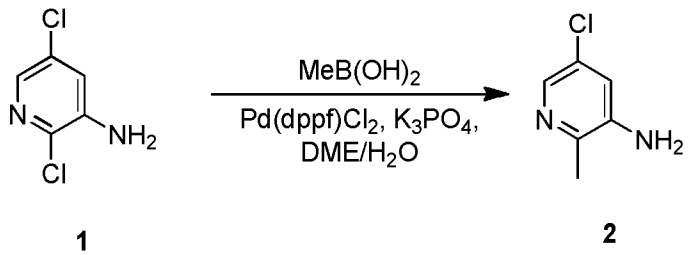
Example 122. MPL-234

Scheme





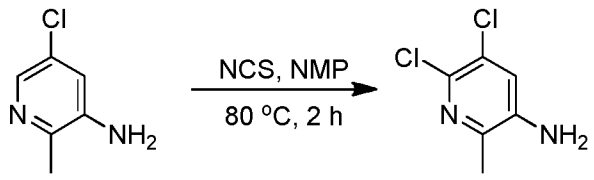
Synthesis of 5-chloro-2-methyl-pyridin-3-amine



To a solution of 2,5-dichloropyridin-3-amine (5 g, 30.67 mmol, 1 *eq*), methylboronic acid (2.75 g, 46.01 mmol, 1.5 *eq*), K_3PO_4 (19.53 g, 92.02 mmol, 3 *eq*) in DME (45 mL) and H_2O (5 mL) was added $Pd(dppf)Cl_2$ (2.24 g, 3.07 mmol, 0.1 *eq*), the mixture was stirred at 120 °C for 12 hr under N_2. LCMS showed the mixture was consumed completely. The mixture was filtered and

the filter was concentrated under reduced pressure to give the residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc=1 : 0 to 3 : 1). The product 5-chloro-2- methyl-pyridin-3-amine (2.3 g, 14.52 mmol, 47.33% yield, 90% purity) was obtained as a green solid (LCMS (ESI) m/z 142.9 $[M+H]^+$.

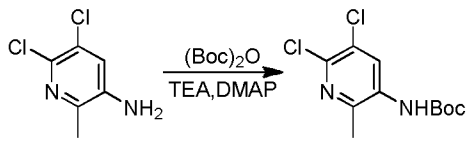
Synthesis of 5,6-dichloro-2-methyl-pyridin-3-amine



2 3

To a solution of 5-chloro-2-methyl-pyridin-3-amine (2.4 g, 16.83 mmol, 1 *eq*) in NMP (25 mL) was added NCS (2.36 g, 17.67 mmol, 1.05 *eq*) under N_2, the mixture was stirred for 2 h under 80 °C. TLC showed the reactant 2 was consumed completely. The mixture was poured into 200 mL ice-water and extracted with EtOAc (2 x 200 mL), dried and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 2 : 1). The product 5,6-dichloro-2- methyl-pyridin-3-amine (2.1 g, 10.68 mmol, 63.43% yield, 90% purity) was obtained as a white solid.

Synthesis of tert-butyl N-(5,6-dichloro-2-methyl-3-pyridyl)carbamate

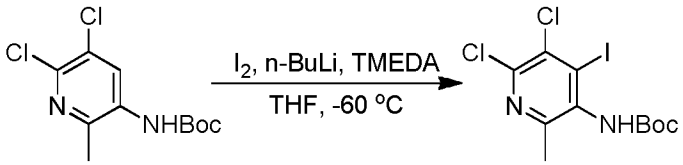


3 4

5,6-dichloro-2-methyl-pyridin-3-amine (1 g, 5.65 mmol, 1 *eq*) in THF (10 mL) was added Boc_2O (1.85 g, 8.47 mmol, 1.95 mL, 1.5 *eq*). Then TEA (1.71 g, 16.95 mmol, 2.36 mL, 3 *eq*) and DMAP (138.02 mg, 1.13 mmol, 0.2 *eq*) was added to above solution and stirred at 10 °C for 12 hr. TLC indicated one major new spot with larger polarity and lower polarity was detected. The reaction was concentrated under reduced pressure to remove solvent. Then the residue was dissolved by EtOAc (20 mL) and washed by H_2O (20 mL) and washed by brine (20 mL). The

organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1 : 0 to 10 : 1). Compound tert-butyl N-(5,6-dichloro -2-methyl-3-pyridyl)carbamate (600 mg, 1.95 mmol, 34.52% yield, 90% purity) was obtained as a white solid.

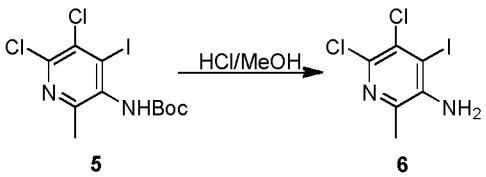
Synthesis of ethyl tert-butyl N-(5,6-dichloro-4-iodo-2-methyl-3-pyridyl)carbamate



4 **5**

tert-butyl N-(5,6-dichloro-2-methyl-3-pyridyl)carbamate (300 mg, 1.08 mmol, 1 *eq*) and TMEDA (251.57 mg, 2.16 mmol, 326.72 uL, 2 *eq*) in THF (5 mL) (dry) was cooled to -60 °C. Then n-BuLi (2.5 M, 1.08 mL, 2.5 *eq*) was added dropwise to above solution at -60 °C and stirred at -60 °C for 1 hr. I_2 (412.10 mg, 1.62 mmol, 327.07 uL, 1.5 *eq*) in dry THF (5 mL) was added dropwise to above solution at -60 °C and stirred at -60 °C for 1 hr. LCMS showed the desired mass was detected. The reaction was washed by sat. NH_4Cl (10 mL), washed by sat. Na_2SO_3 (10 mL). The mixture was concentrated under reduced pressure to remove solvent. Then the mixture was extracted with EtOAc (10 mL x 2). The organic phase was concentrated under reduced pressure. Compound tert-butyl N-(5,6-dichloro-4-iodo-2-methyl-3-pyridyl)carbamate (436 mg, crude) was obtained as yellow oil.

Synthesis of 5,6-dichloro-4-iodo-2-methyl-pyridin-3-amine

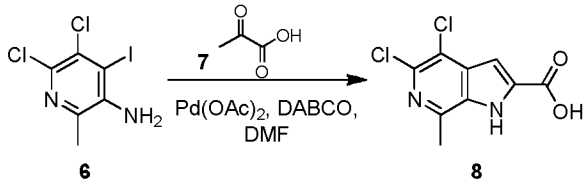


5 **6**

tert-butyl N-(5,6-dichloro-4-iodo-2-methyl-3-pyridyl)carbamate (436 mg, 1.08 mmol, 1 *eq*) in HCl/MeOH (4 M, 4 mL, 14.79*eq*) was stirred at 10 °C for 30 min. LCMS showed 30 % desired mass. Then the reaction was added HCl/MeOH (4 M, 2 mL). TLC indicated one major new spot with larger polarity was detected. The reaction was concentrated under reduced pressure.

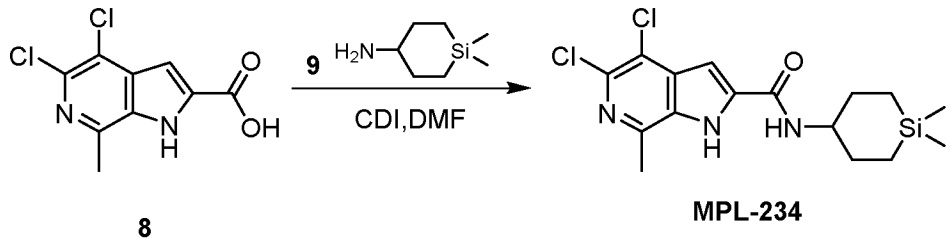
The mixture was washed by sat. Na_2CO_3 (25 mL) and extracted with EtOAc (20 mL x 2). The organic phase was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1 : 0 to 3 : 1). Compound 5,6-dichloro-4-iodo-2-methyl-pyridin-3-amine (113 mg, 354.38 umol, 32.76% yield, 95% purity) was obtained as a yellow solid.

Synthesis of 4,5-dichloro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



A mixture of 5,6-dichloro-4-iodo-2-methyl-pyridin-3-amine (113 mg, 373.03 umol, 1 *eq*), 2-oxopropanoic acid (65.70 mg, 746.05 umol, 52.56 uL, 2 *eq*), DABCO (83.69 mg, 746.05 umol, 82.05 uL, 2 *eq*) and $Pd(OAc)_2$ (16.75 mg, 74.61 umol, 0.2 *eq*) in DMF (3 mL) under N_2 was stirred at 110 °C for 12 hr. LCMS showed the desired product was detected. The mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved with H_2O (5 mL) and neutralized with 6 M HCl to pH = 3. Then the precipitate was formed, and the suspension was filtered and the filter cake was washed with water (5 mL), collected and lyophilized. Compound 4,5-dichloro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (90 mg, 348.89 umol, 93.53% yield, 95% purity) was obtained as a brown solid. LCMS (ESI), m/z 244.9$[M+H]^+$

Synthesis of 4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-7-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide

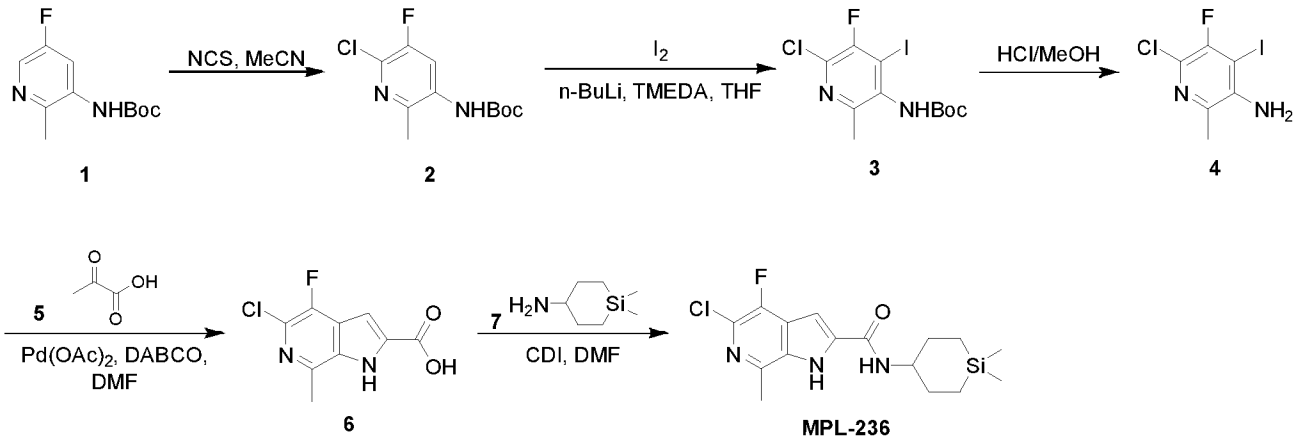


A solution of 4,5-dichloro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 204.03 umol, 1 *eq*) and CDI (39.70 mg, 244.84 umol, 1.2 *eq*) in DMF (1.5 mL) was stirred at 30 °C for 0.5 hr. LCMS showed the desired product was detected. 1,1-dimethylsilinan-4-amine (34.96 mg, 243.97 umol, 1.2 *eq*) was added to above step solution (60 mg, 203.30 umol, 1 *eq*) in DMF (0.5 mL) was stirred at 30 °C for 1 hr. LCMS showed the desired product was detected. The mixture was not work up and purified by prep-HPLC. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 65%-88%,11min). Compound 4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-7-methyl-1H-pyrrolo [2,3-c]pyridine-2-carboxamide (9 mg, 24.30 umol, 11.95% yield, 100% purity) was obtained as a white solid (LCMS (ESI), m/z 370.0[M+H]$^+$).

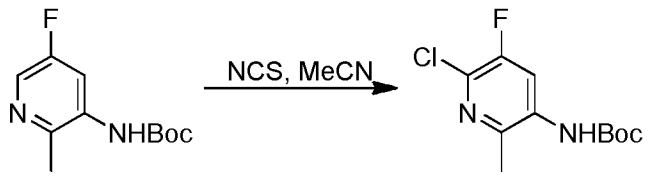
^{1}H NMR (500MHz, DMSO-d6) δ = 12.48 (br s, 1H), 8.51 (br d, *J*=7.9 Hz, 1H), 7.19 (s, 1H), 3.77 - 3.58 (m, 1H), 2.61 (s, 3H), 1.97 - 1.82 (m, 2H), 1.67 - 1.39(m, 2H), 0.69 (br d, *J*=14.6 Hz, 2H), 0.53 (dt, *J*=4.7, 14.1 Hz, 2H), 0.07 - 0.11 (m, 6H).

Example 123. MPL-236

Scheme



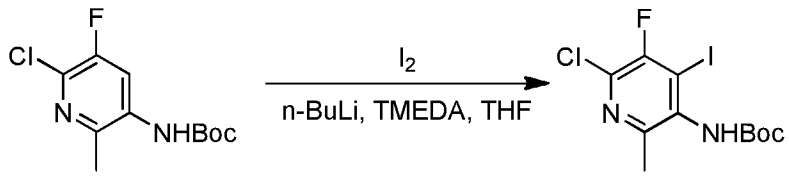
Synthesis of tert-butyl N-(6-chloro-5-fluoro-2-methyl-3-pyridyl)carbamate



1 2

To a solution of tert-butyl N-(5-fluoro-2-methyl-3-pyridyl)carbamate (1 g, 4.42 mmol, 1 *eq*) in MeCN (10 mL) was added NCS (619.72 mg, 4.64 mmol, 1.05 *eq*) at 0 °C. The mixture was stirred at 65 °C for 16 hr. TLC indicated one major new spot with lower polarity was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/Petroleum ether gradient at 30 mL/min). Compound tert-butyl N-(6-chloro-5-fluoro-2-methyl-3-pyridyl)carbamate (600 mg, 2.19 mmol, 49.47% yield, 95% purity) was obtained as a yellow solid.

Synthesis of tert-butyl N-(6-chloro-5-fluoro-4-iodo-2-methyl-3-pyridyl) carbamate

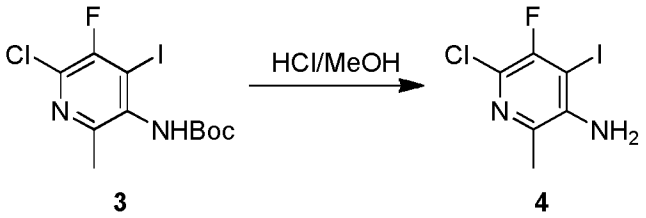


2 3

To a solution of tert-butyl N-(6-chloro-5-fluoro-2-methyl-3-pyridyl)carbamate (600 mg, 2.30 mmol, 1 *eq*) in THF (10 mL) was added TMEDA (534.91 mg, 4.60 mmol, 694.68 uL, 2 *eq*). The mixture was added n-BuLi (2.5 M, 1.84 mL, 2 *eq*) at -78 °C. The reaction mixture was stirred at -78 °C for 0.5 hr. Then a solution of I_2 (1.17 g, 4.60 mmol, 927.23 uL, 2 *eq*) in THF (5 mL) was added. Then reaction mixture was stirred at -78 °C for 1 hr. TLC indicated one major new spot with larger polarity was detected. The reaction mixture was quenched by addition sat. aq. NH_4Cl 15 mL at -78 °C, and then diluted with H_2O 20 mL and extracted with EtOAc 60 mL (20 mL x **3**). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~25% EtOAc/Petroleum ether

gradient at 30 mL/min). Compound tert-butyl N-(6-chloro-5-fluoro-4-iodo-2-methyl-3-pyridyl)carbamate (870 mg, 2.03 mmol, 88.00% yield, 90% purity) was obtained as a yellow solid (LCMS m/z: 386.9$[M+H]^+$).

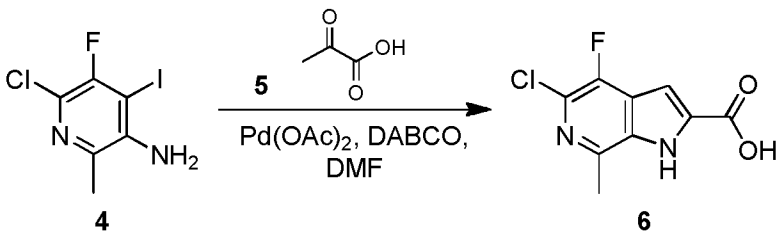
Synthesis of 6-chloro-5-fluoro-4-iodo-2-methyl-pyridin-3-amine



3 4

A mixture of tert-butyl N-(6-chloro-5-fluoro-4-iodo-2-methyl-3-pyridyl)carbamate (400 mg, 1.03 mmol, 1 *eq*) in HCl/MeOH (4 M, 10.00 mL, 38.66 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 30 °C for 4 hr under N_2 atmosphere. TLC indicated one major new spot with larger polarity was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The crude product was used to next step directly. Compound 6-chloro-5-fluoro-4-iodo-2-methyl-pyridin-3-amine (300 mg, crude) was obtained as a yellow solid.

Synthesis of 5-chloro-4-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

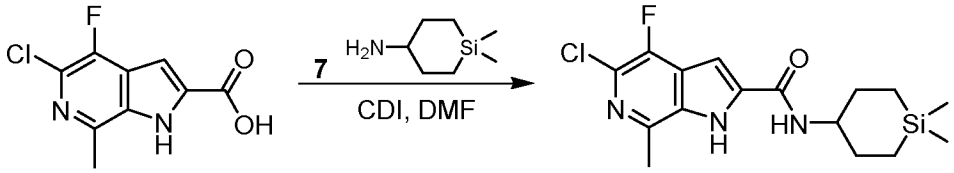


4 6

A mixture of 6-chloro-5-fluoro-4-iodo-2-methyl-pyridin-3-amine (300 mg, 1.05 mmol, 1 *eq*), 2-oxopropanoic acid (184.44 mg, 2.09 mmol, 147.55 uL, 2 *eq*), $Pd(OAc)_2$ (47.02 mg, 209.44 umol, 0.2 *eq*), DABCO (234.94 mg, 2.09 mmol, 230.33 uL, 2 *eq*) in DMF (8 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 110 °C for 12 hr under N_2 atmosphere. LC-MS indicated desired mass was detected. The reaction mixture was diluted with H_2O 10 mL and extracted with EtOAc 30 mL (10 mL x 3). The combined organic layers

were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150x30mmx4um; mobile phase: [water (0.05%HCl)-ACN]; B%: 28%-48%,10min). Compound 5-chloro-4-fluoro-7-methyl-1H-pyrrolo [2,3-c]pyridine-2-carboxylic acid (110 mg, 481.17 umol, 45.95% yield) was obtained as brown solid.

Synthesis of 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-7-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



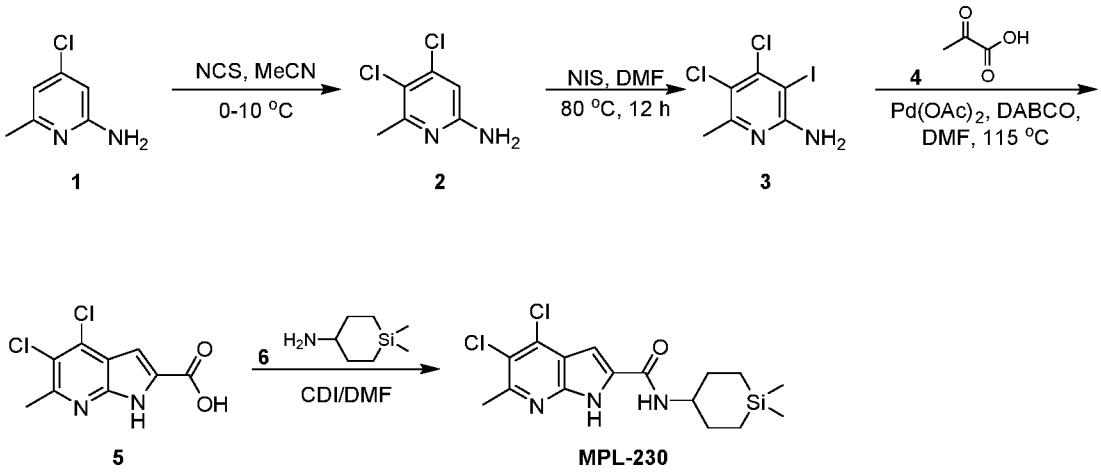
6 **MPL-236**

To a solution of 5-chloro-4-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 218.72 umol, 1 *eq*) in DMF (1 mL) was added CDI (53.20 mg, 328.07 umol, 1.5 *eq*). The mixture was stirred at 25 °C for 2 hr. Then the reaction mixture was added 1,1-dimethylsilinan-4-amine (47.01 mg, 328.07 umol, 1.5 *eq*). The reaction mixture was stirred at 25 °C for 12 hr. LC-MS indicated desired mass was detected. The reaction mixture was drop into water and the product was dissolved out, filtered and dry. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% EtOAc/Petroleum ether gradient at 35 mL/min). Compound 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-7-methyl- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide (21.1 mg, 58.29 umol, 26.65% yield, 97.759% purity) was obtained as a white solid (LCMS m/z: 354.0 $[M+H]^+$).

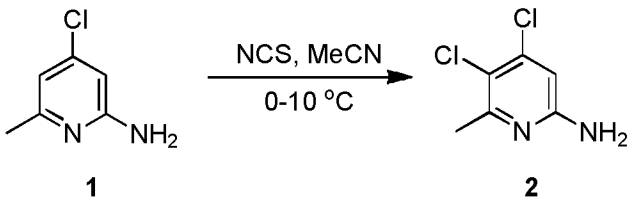
^{1}H NMR (400 MHz, METHANOL-*d*4) δ= 7.20 (s, 1 H), 3.80 (br t, *J*=11.2 Hz, 1 H), 2.70 (s, 3 H), 2.09 - 2.20 (m, 2 H), 1.61 - 1.74 (m, 2 H), 0.80 - 0.90 (m, 2H), 0.64 - 0.77 (m, 2 H), 0.12 (s, 3 H), 0.05 (s, 3 H).

Example 124. MPL-230

Scheme

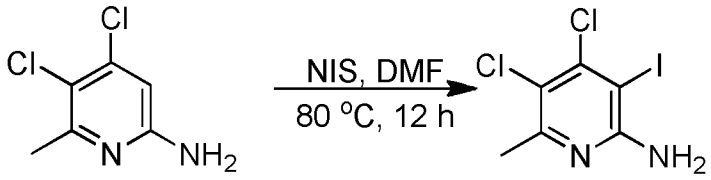


Synthesis of 4,5-dichloro-6-methyl-pyridin-2-amine



To a solution of 4-chloro-6-methyl-pyridin-2-amine (2.40 g, 16.83 mmol, 1 *eq*) in MeCN (25 mL) was batch-wise added NCS (2.36 g, 17.67 mmol, 1.05 *eq*) at -20 °C under N_2, then the temperature was allowed up to 20 °C and the mixture was stirred for 12 h under the same condition. TLC showed the reactant 1 was consumed. The reaction was quenched by addition of water (30 mL). Then extracted with EtOAc (3 x 50 ml), the organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 5:1). The product 4,5-dichloro-6-methyl-pyridin-2-amine (1.4 g, 7.12 mmol, 42.29% yield, 90% purity) was obtained as brown solid.

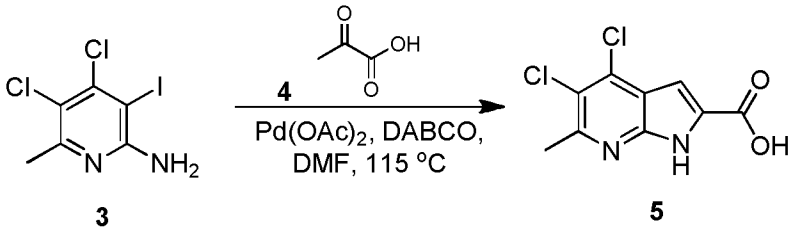
Synthesis of 4,5-dichloro-3-iodo-6-methyl-pyridin-2-amine



2 3

To a solution of 4,5-dichloro-6-methyl-pyridin-2-amine (1.4 g, 7.91 mmol, 1 *eq*) in DMF (15 mL) was added NIS (3.56 g, 15.82 mmol, 2 *eq*) under N_2. The mixture was stirred for 12 hr under 80 °C. LCMS and TLC showed the reactant 2 was consumed. The mixture was added to water (150 ml) and filtered, the filter cake was solved by EtOAc and the filter was extracted with EtOAc (3 x 50 mL). The combined organic phase dried and evaporated. The residue was purified by column chromatography (SiO_2, Petroleum ether/EtOAc=1:0 to 5:1). The product 4,5-dichloro-3-iodo-6-methyl-pyridin-2-amine (1.3 g, 3.00 mmol, 37.99% yield, 70% purity) was obtained as orange solid.

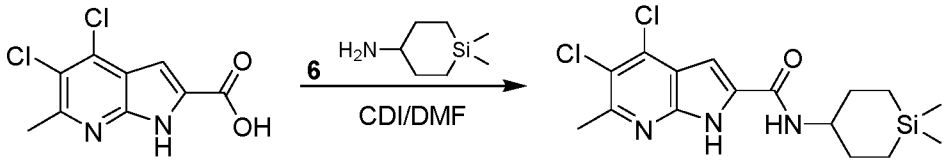
Synthesis of 4,5-dichloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



3 5

To a solution of 4,5-dichloro-3-iodo-6-methyl-pyridin-2-amine (800 mg, 2.64 mmol, 1 *eq*) in DMF (15 mL) was added ethyl 2-oxopropanoate (657.10 mg, 3.96 mmol, 625.81 uL, 1.5 *eq*), DABCO (592.48 mg, 5.28 mmol, 580.86 uL, 2 *eq*) and $Pd(OAc)_2$ (118.58 mg, 528.18 umol, 0.2 *eq*). The mixture was stirred at 115 °C for 4 hr under N_2. LCMS showed the reactant 3 was consumed and the desired mass was detected. The mixture was concentrated under reduced pressure to remove the solvent, then dissolved with NaOH (2M, 20 ml), filtered and the filter was acidified with HCl (6m) to pH=4, filter to give the crude product. The crude product was used for the next step without the further purification. The crude product 4,5-dichloro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylic acid (250 mg, 816.12 umol, 30.90% yield, 80% purity) was obtained as brown solid (LCMS (ESI) m/z 227 $[M-H_2O]^+$).

Synthesis of 4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



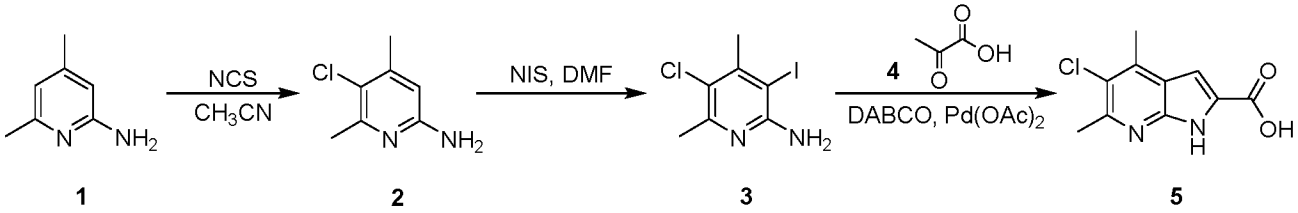
5 **MPL-230**

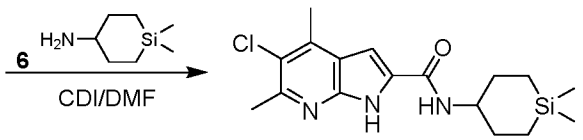
To a solution of 4,5-dichloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 408.06 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (99.25 mg, 612.09 umol, 1.5 *eq*), the mixture was stirred at 30 °C for 0.5 h, then the 1,1-dimethylsilinan-4-amine (87.71 mg, 612.09 umol, 1.5 *eq*) was added, then the mixture was stirred at 30 °C for 0.5 h. LCMS showed the reactant 5 was consumed completely and the desired mass was detected. The mixture was added to water (15 mL) and stirred for 10min, filtered and the filter cake was dried under reduced pressure. The crude product was purity by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: [water(0.05%HCl)-ACN];B%: 70%-90%,10min). The product 4,5-dichloro-N-(1,1-dimethylsilinan -4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (21.6 mg, 57.82 umol, 14.17% yield, 99.137% purity) was obtained as brown solid (LCMS (ESI) m/z 370.0 $[M+H]^+$).

^{1}H NMR (400MHz, DMSO-d_6) δ =12.49 (s, 1H), 8.39 (d, *J*=7.8 Hz, 1H), 7.19 (d, *J*=2.0 Hz, 1H), 3.70 (br s, 1H), 2.63 (s, 3H), 1.96 (br s, 2H), 1.65 - 1.50 (m, 2H), 0.76 (br d, *J*=14.9 Hz, 2H), 0.65 - 0.54 (m, 2H), 0.07 (s, 3H), 0.02 (s, 3H).

Example 125. MPL-239

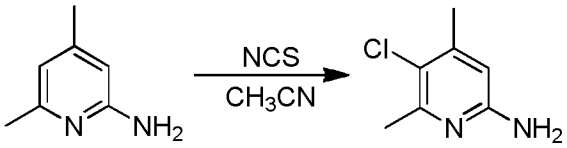
Scheme





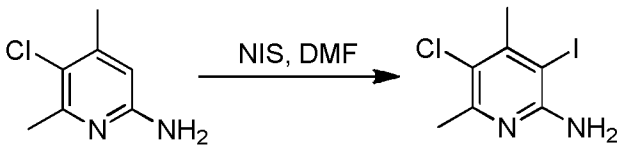
MPL-239

5-chloro-4,6-dimethyl-pyridin-2-amine



To a solution of 4,6-dimethylpyridin-2-amine (4 g, 32.74 mmol, 1 *eq*) in CH_3CN (40 mL) was added NCS (4.59 g, 34.38 mmol, 1.05 *eq*) at 0°C. The mixture was stirred at 10 °C for 12 h. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure and diluted with DCM (30 mL) and washed with water (30 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 1 : 0 to 3 : 1). The product 5-chloro-4,6-dimethyl-pyridin-2-amine (3.3 g, 18.96 mmol, 57.92% yield, 90% purity) was obtained as a yellow solid (LCMS (ESI) m/z 305.1 $[M+H]^+$).

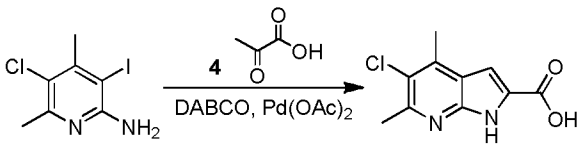
5-chloro-3-iodo-4,6-dimethyl-pyridin-2-amine



2 3

To a solution of 5-chloro-4,6-dimethyl-pyridin-2-amine (3.3 g, 21.07 mmol, 1 *eq*) in DMF (30 mL) was added NIS (11.85 g, 52.68 mmol, 2.5 *eq*) at 0 °C. Then the mixture was stirred at 10 °C for 12 h. LCMS showed the starting material was remained. NIS (3 g) was added. The mixture was stirred at the same temperature for 12 h. LC-MS showed the starting material was consumed completely. The mixture was concentrated in reduced pressure. Then the mixture was diluted with EtOAc (50 mL). It was washed with aqueous 3% LiCl (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc=1 : 0 to 10 : 1). The product 5-chloro-3-iodo-4,6-dimethyl-pyridin-2-amine (2.3 g, 7.73 mmol, 36.71% yield, 95% purity) was obtained as a white solid (LCMS (ESI) m/z 349.1 $[M+H]^+$).

5-chloro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

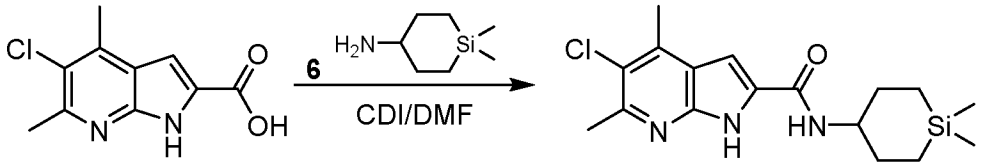


3 5

To a solution of 5-chloro-3-iodo-4,6-dimethyl-pyridin-2-amine (1 g, 3.54 mmol, 1 *eq*), 2-oxopropanoic acid (498.74 mg, 5.66 mmol, 398.99 uL, 1.6 *eq*) and DABCO (794.12 mg, 7.08 mmol, 778.55 uL, 2 *eq*) in DMF (15 mL) was added $Pd(OAc)_2$ (397.35 mg, 1.77 mmol, 0.5 *eq*) under N_2. The reaction was stirred at 115 °C for 4 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (120 mL), acidified with HCl (2 M) to pH = 4. The mixture was filtered and the filter cake was washed with 10 mL x 3 of petroleum ether, dried under reduced pressure to give product. The residue was diluted with CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The product 5-chloro-4,6-dimethyl-1H-

pyrrolo[2,3-b]pyridine-2- carboxylic acid (650 mg, 1.45 mmol, 40.87% yield, 50% purity) was obtained as a black solid (LCMS (ESI) m/z 195.0 $[M+H]^+$).

5-chloro-N-(1,1-dimethylsilinan-4-yl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbox amide



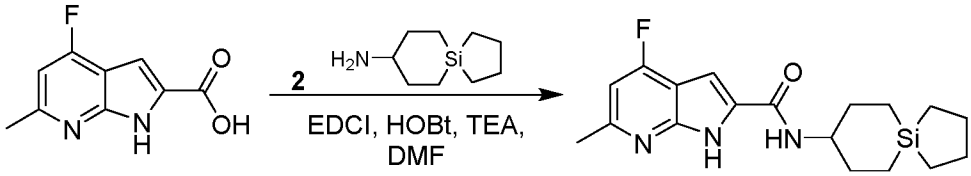
5 **MPL-239**

To a solution of 5-chloro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 445.15 umol, 1 *eq*) in DMF (1 mL) was added CDI (86.62 mg, 534.18 umol, 1.2 *eq*). Then the mixture was stirred at 30 °C for 0.5 h. 1,1-dimethylsilinan-4-amine (76.55 mg, 534.18 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LC-MS showed the starting material was consumed completely. The reaction mixture was added to water (20ml), filtered and the filter cake was washed with 10 mL of water, dried in vacuo to give product. The crude product diluted with EtOAc (10 mL). The residue was purified by prep-TLC (SiO_2, Petroleum ether : EtOAc = 2 : 1). The residue was diluted in CH_3CN (1 mL) and H_2O (10 mL), then lyophilized. The product 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (19.6 mg, 54.95 umol, 12.34% yield, 98.105% purity) was obtained as a white solid (LCMS (ESI) m/z 350.0 $[M+H]^+$).

^{1}H NMR (500MHz, DMSO-d_6) δ= 12.02 (s, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 7.17 (d, *J*=1.8 Hz, 1H), 3.76 - 3.65 (m, 1H), 2.58 (s, 3H), 2.54 (s, 3H), 2.03 - 1.95 (m, 2H), 1.64 - 1.53 (m, 2H), 0.77 (br d, *J*=14.5 Hz, 2H), 0.61 (dt, *J*=4.7, 14.1 Hz, 2H), 0.09 (s, 3H), 0.03 (s, 3H).

Example 126. MPL-253

Synthesis of 4-fluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine -2-carboxamide



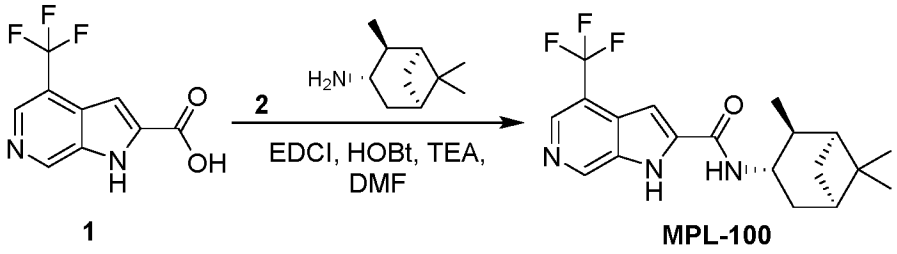
1 MPL-253

To a solution of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 515.03 umol, 1 *eq*) in DMF (1 mL) was added 5-silaspiro[4.5]decan-8-amine (137.79 mg, 669.54 umol, 1.3 *eq*, HCl). Then a solution of HOBt (208.77 mg, 1.55 mmol, 3 *eq*) and EDCI (296.20 mg, 1.55 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (156.35 mg, 1.55 mmol, 215.06 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN];B%: 60%-88%,11min). Compound 4-fluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (30 mg, 85.78 umol, 16.66% yield, 98.79% purity) was obtained as a yellow solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 346.1 $[M+H]^+$).

^{1}H NMR (500MHz, CHLOROFORM-*d*) δ= 9.49 (br s, 1H), 6.78 (s, 1H), 6.73 (d, *J*=10.5 Hz, 1H), 6.04 (br d, *J*=7.9 Hz, 1H), 4.00 - 3.91 (m, 1H), 2.64 (s,3H), 2.25 (br dd, *J*=4.6, 7.8 Hz, 2H), 1.66 - 1.60 (m, 5H), 1.66 - 1.60 (m, 1H), 0.88 - 0.79 (m, 4H), 0.63 (br t, *J*=7.2 Hz, 2H), 0.59 (br t, *J*=7.3 Hz, 2H).

Example 127. MPL-100

Synthesis of 4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

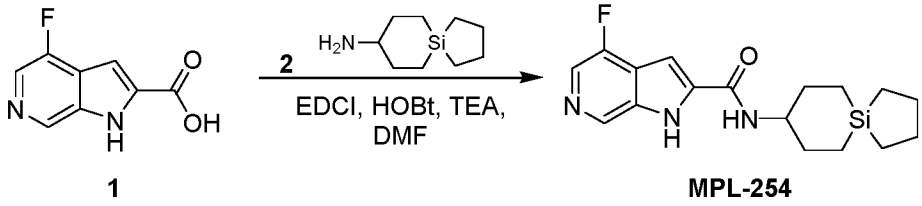


To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 434.51 umol, 1 *eq*) in DMF (1 mL) was added (1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-amine (86.57 mg, 564.87 umol, 1.3 *eq*). Then a solution of HOBt (176.13 mg, 1.30 mmol, 3 *eq*) and EDCI (249.89 mg, 1.30 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (131.90 mg, 1.30 mmol, 181.44 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc (30 mL). It was washed with sat. aq. $NaHCO_3$ (10 mL x 2), aqueous 5% LiCl (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was delivered without further purification. Compound 4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide (92.9 mg, 249.42 umol, 57.40% yield, 98.10% purity) was obtained as a yellow solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 366.1 $[M+H]^+$).

^{1}H NMR (500MHz, DMSO-d_6) δ= 9.03 (s, 1H), 8.77 (br s, 1H), 8.50 (br s, 1H), 7.45 (br s, 1H), 4.48 - 4.39 (m, 1H), 2.17 - 2.06 (m, 2H), 1.97 (br s, 1H), 1.84(br s, 1H), 1.74 (br dd, *J*=6.3, 12.9 Hz, 1H), 1.27 - 1.21 (m, 5H), 1.10 - 1.06 (m, 6H).

Example 128. MPL-254

Synthesis of 4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine -2-carboxamide



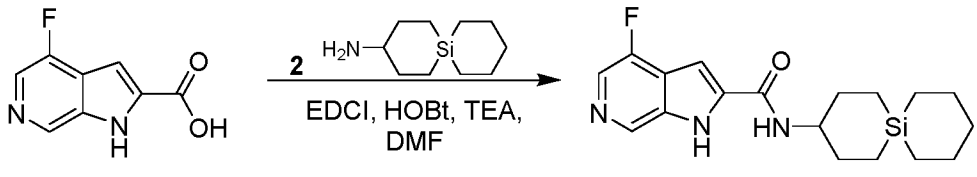
1 MPL-254

To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added 5-silaspiro[4.5]decan-8-amine (125.67 mg, 610.65 umol, 1.1 *eq*, HCl). Then a solution of HOBt (225.03 mg, 1.67 mmol, 3 *eq*) and EDCI (319.26 mg, 1.67 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (168.52 mg, 1.67 mmol, 231.81 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The residue was delivered without further purification. Compound 4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (135.7 mg, 387.58 umol, 69.82% yield, 94.67% purity) was obtained as a gray solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 332.1 $[M+H]^+$).

^{1}H NMR (500MHz, DMSO-d_6) δ = 12.43 (br s, 1H), 8.66 (d, J=2.6 Hz, 1H), 8.55 (d, J=8.1 Hz, 1H), 8.09 (d, J=1.8 Hz, 1H), 7.34 (s, 1H), 3.85 - 3.74 (m, 1H),2.09 (br d, J=9.0 Hz, 2H), 1.67 - 1.55 (m, 6H), 0.84 - 0.73 (m, 4H), 0.63 (br t, J=6.7 Hz, 2H), 0.55 (br t, J=6.7 Hz, 2H).

Example 129. MPL-259

Synthesis of 4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



1 MPL-259

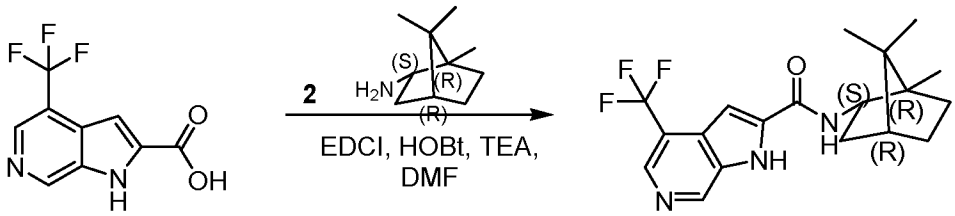
To a solution of 4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 555.14 umol, 1 *eq*) in DMF (1 mL) was added 6-silaspiro[5.5]undecan-3-amine (134.24 mg, 610.65 umol, 1.1

eq, HCl). Then a solution of HOBt (225.03 mg, 1.67 mmol, 3 *eq*) and EDCI (319.26 mg, 1.67 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (168.52 mg, 1.67 mmol, 231.81 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted with EtOAc (30 mL). It was washed with sta. aq. $NaHCO_3$ (10 mL x 2), aqueous 5% LiCl (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was delivered without further purification. Compound 4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (96.6 mg, 270.10 umol, 48.65% yield, 96.60% purity) was obtained as a yellow solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 346.1 $[M+H]^+$).

^{1}H NMR (500MHz, DMSO-d_6) δ= 8.65 (d, *J*=2.6 Hz, 1H), 8.55 (br d, *J*=8.2 Hz, 1H), 8.09 (d, *J*=1.7 Hz, 1H), 7.33 (s, 1H), 3.81 - 3.71 (m, 1H), 2.02 (br d,*J*=9.3 Hz, 2H), 1.69 - 1.58 (m, 6H), 1.39 (br s, 2H), 0.92 (br d, *J*=14.5 Hz, 2H), 0.74 - 0.68 (m, 2H), 0.64 - 0.57 (m, 4H).

Example 130. MPL-190

Synthesis of 4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



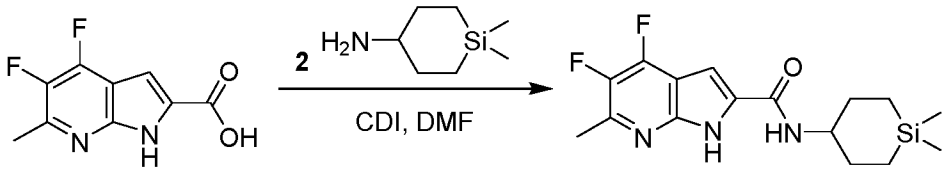
To a solution of 4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 434.51 umol, 1 *eq*) in DMF (1 mL) was added 1,7,7-trimethylnorbornan-2-amine (86.57 mg, 564.86 umol, 1.3 *eq*). Then a solution of HOBt (176.13 mg, 1.30 mmol, 3 *eq*) and EDCI (249.89 mg, 1.30 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (131.90 mg, 1.30 mmol, 181.44 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL).

There was much precipitation which was collected by filter. The cake was diluted with EtOAc (30 mL). It was washed with sat. aq. $NaHCO_3$ (10 mL x 2), aqueous 5% LiCl (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was delivered without further purification. Compound 4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (62.3 mg, 166.68 umol, 38.36% yield, 97.76% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 366.1 $[M+H]^+$).

^{1}H NMR (400MHz, DMSO-d_6) δ= 12.62 (br s, 1H), 9.00 (s, 1H), 8.50 - 8.42 (m, 2H), 7.51 (br s, 1H), 4.42 (br s, 1H), 2.21 (br t, *J*=11.7 Hz, 1H), 1.80 - 1.66(m, 3H), 1.47 - 1.38 (m, 1H), 1.31 - 1.23 (m, 1H), 1.18 (dd, *J*=4.9, 13.1 Hz, 1H), 0.97 (s, 3H), 0.87 (s, 3H), 0.78 (s, 3H).

Example 131. MPL-229

Synthesis of N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b] pyridine-2-carboxamide



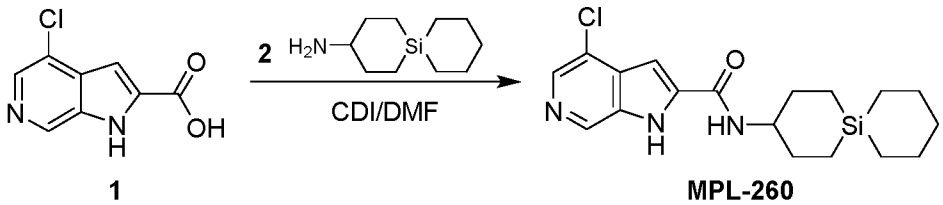
MPL-229

To a solution of 4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b] pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (33.63 mg, 207.40 umol, 1.1 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 1, 1-dimethylsilinan-4-amine (29.72 mg, 207.40 umol, 1.1 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. LCMS showed there were main desired compound and a little starting material. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was transferred in bottom flask. The crude product was purified by prep-TLC (SiO_2, Petroleum ether: EtOAc =5:1). Compound N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b] pyridine-2- carboxamide (30 mg, 88.39 umol, 46.88% yield, 99.423% purity) was obtained as a white solid (LCMS (ESI), m/z 338.0$[M+H]^+$).

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 9.55 (br s, 1H), 6.80 (s, 1H), 6.04 (br d, *J*=8.2 Hz, 1H), 3.91 (br d, *J*=8.2 Hz, 1H), 2.63 (d, *J*=3.1 Hz, 3H), 2.18(br d, *J*=10.2 Hz, 2H), 1.59 - 1.53 (m, 2H), 0.83 - 0.68 (m, 4H), 0.10 (s, 3H), 0.06 (s, 3H).

Example 132. MPL-260

Synthesis of 4-chloro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2 – carboxamide



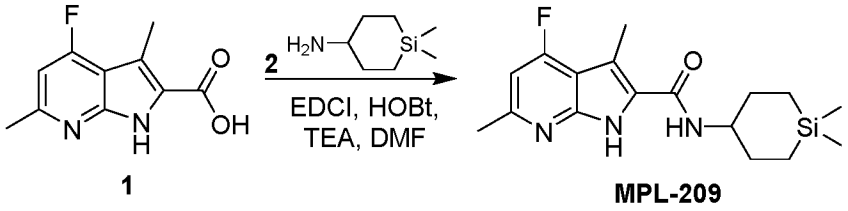
1 **MPL-260**

To a solution of 4-chloro-1H-pyrrolo [2, 3-c] pyridine-2-carboxylic acid (50 mg, 254.34 umol, 1 *eq*) in DMF (1.5 mL) was added CDI (49.49 mg, 305.20 umol, 1.2 *eq*). The mixture was stirred at 30 °C for 0.5 h. Then 6-silaspiro[5.5]undecan-3-amine (55.96 mg, 305.20 umol, 1.2 *eq*) was added. The mixture was stirred at 30 °C for 11.5 h. TLC (Petroleum ether : EtOAc = 5 : 1, R_f = 0.5) showed there were no starting material and one major new spot with higher polarity was detected. The reaction was added dropwise to H_2O (20 mL). The precipitation was collected by filter. The cake was transferred in bottom flask. The residue was purified by column chromatography (SiO_2, Petroleum ether : EtOAc = 5 : 1). Compound 4-chloro-N-(6-silaspiro [5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (8.6 mg, 23.73 umol, 9.33% yield, 99.880% purity) was obtained as a yellow solid (LCMS (ESI), m/z 362.0 $[M+H]^+$).

1H NMR (500MHz, CHLOROFORM-d) δ = 10.82 (br s, 1H), 8.85 (s, 1H), 8.29 (s, 1H), 6.93 (s, 1H), 6.29 (br d, *J*=7.3 Hz, 1H), 4.01 (br d, *J*=8.2 Hz, 1H),2.25 (br d, *J*=9.5 Hz, 2H), 1.76 - 1.64 (m, 6H), 1.43 (br s, 2H), 0.95 (br d, *J*=15.0 Hz, 2H), 0.79 - 0.69 (m, 4H), 0.68 - 0.62 (m, 2H).

Example 133. MPL-209

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

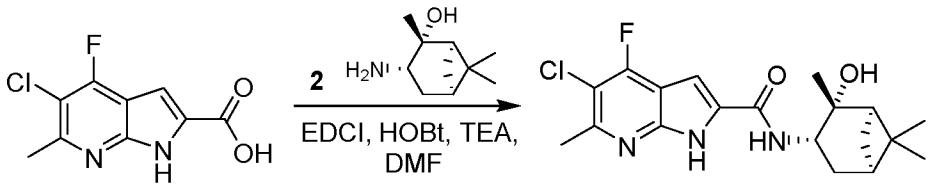


To a solution of 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (60 mg, 288.20 umol, 1 *eq*) in DMF (0.5 mL) was added 1,1-dimethylsilinan-4-amine (53.69 mg, 374.66 umol, 1.3 *eq*). Then a solution of HOBt (116.82 mg, 864.60 umol, 3 *eq*) and EDCI (165.74 mg, 864.60 umol, 3 *eq*) in DMF (0.5 mL) was added followed by TEA (87.49 mg, 864.60 umol, 120.34 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were main starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was diluted in CH_3CN (5 mL) and H_2O (20 mL), then lyophilized. The crude product was purified by silica column chromatography (eluent of 0~30% EtOAc/Petroleum ether gradient, 4 g silica column). All fractions found to contain the product by TLC (Petroleum ether : EtOAc = 3 : 1, R_f = 0.3) were combined and evaporated. Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbox amide (30 mg, 86.66 umol, 30.07% yield, 96.33% purity) was obtained as a white solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 334.1 $[M+H]^+$).

^{1}H NMR (400MHz, METHANOL-d_4) δ= 6.75 (d, *J*=11.3 Hz, 1H), 3.78 (br t, *J*=11.3 Hz, 1H), 2.62 (s, 3H), 2.56 (s, 3H), 2.17 (br d, *J*=12.9 Hz, 2H), 1.71 -1.60 (m, 2H), 0.88 - 0.80 (m, 2H), 0.76 - 0.67 (m, 2H), 0.12 (s, 3H), 0.05 (s, 3H).

Example 134. MPL-220

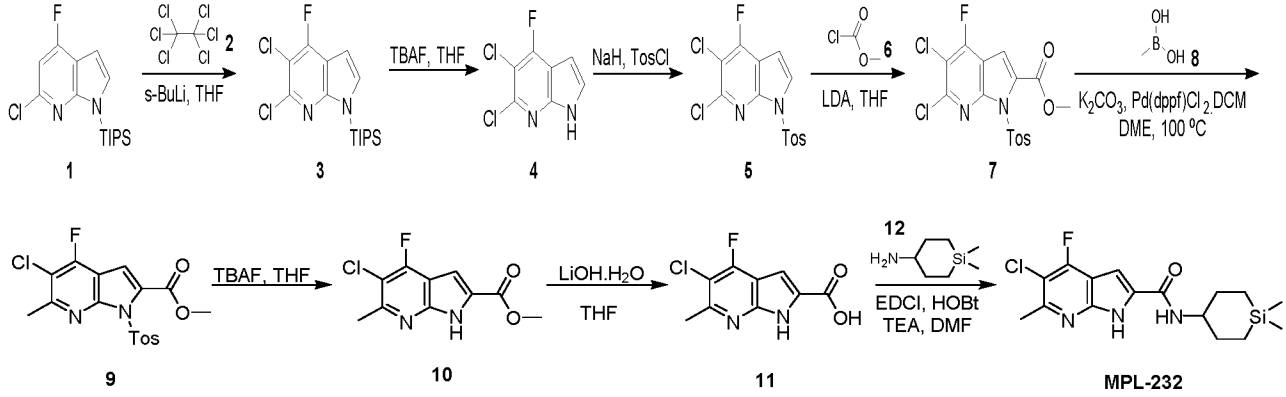
Synthesis of 5-chloro-4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



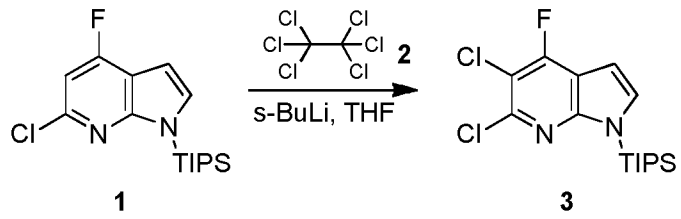
To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (120 mg, 524.92 umol, 1 *eq*) in DMF (1 mL) was added (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan -2-ol (115.50 mg, 682.39 umol, 1.3 *eq*). Then a solution of HOBt (212.78 mg, 1.57 mmol, 3 *eq*) and EDCI (301.88 mg, 1.57 mmol, 3 *eq*) in DMF (1 mL) was added followed by TEA (159.35 mg, 1.57 mmol, 219.19 uL, 3 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed there were starting material and desired compound. The reaction was added dropwise to H_2O (20 mL). There was much precipitation which was collected by filter. The cake was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: [water(0.225%FA)-ACN]; B%: 51%-80%,11min). Compound 5-chloro-4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-tri methyl-norpinan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (11 mg, 28.74 umol, 5.48% yield, 99.25% purity) was obtained as a yellow solid which was confirmed by LCMS and ^{1}H NMR (LCMS (ESI) m/z 380.1 $[M+H]^+$). ^{1}H NMR (500MHz, CHLOROFORM-d) δ= 9.57 (br s, 1H), 7.30 (br d, J=7.5 Hz, 1H), 6.88 (d, J=2.1 Hz, 1H), 4.55 - 4.49 (m, 1H), 2.72 (s, 3H), 2.72 - 2.66(m, 1H), 2.32 - 2.27 (m, 1H), 2.08 - 2.02 (m, 2H), 1.64 (dt, J=2.0, 6.9 Hz, 1H), 1.45 (d, J=10.4 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.12 (s, 3H).

Example 135. MPL-232

Scheme

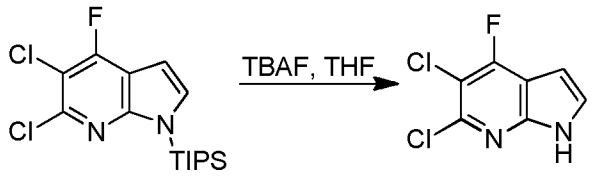


Synthesis of (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



A mixture of (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (10.72 g, 32.79 mmol, 1 eq) in THF (100 mL) was degassed and purged with N_2 for 3 times. s-BuLi (1.3 M in n-hexane, 47.93 mL, 1.9 eq) was added stirred at -60 °C and the reaction was stirred at -60 °C for 30 min under N_2 atmosphere. Then a solution of 1,1,1,2,2,2-hexachloroethane (11.64 g, 49.19 mmol, 5.57 mL, 1.5 eq) in THF (20 mL) was added, and the mixture was stirred -60 °C for 30 min. LC-MS showed desired mass. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 25 °C, and then diluted with water (50 mL) and extracted with petroleum ether (100 mL x 2). The combined organic layer dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether) to afford (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9.14 g, 20.24 mmol, 61.73% yield, 80% purity) as a yellow oil. ^1H NMR was recorded.

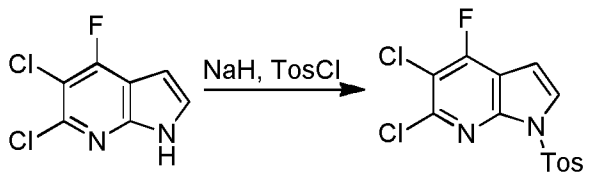
Synthesis of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine



3 4

To a solution of (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9.14 g, 25.30 mmol, 1 eq) in THF (100 mL) was added TBAF (1 M in THF, 30.37 mL, 1.2 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated reactant 3 was consumed completely. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with water (50 mL) at 25 °C for 30 min and filtered. The cake was collected and triturated with petroleum ether (50 mL) at 25 °C for 30 min and filtered. The cake was collected and triturated with CH_3CN (50 mL) at 25 °C for 30 min, and then filtered to afford 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (4.23 g, 16.51 mmol, 65.23% yield, 80% purity) as a yellow solid. ^1H NMR was recorded.

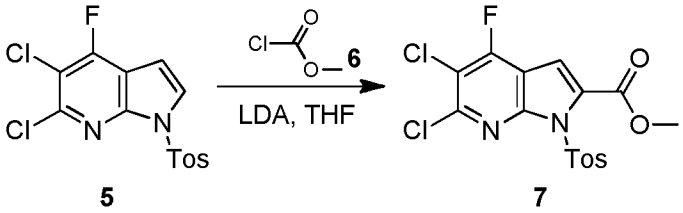
Synthesis of 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



4 5

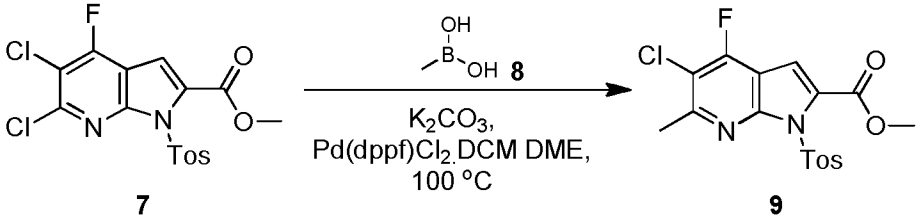
To a cooled solution of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (5.82 g, 28.39 mmol, 1 eq) in THF (70 mL) was added NaH (1.70 g, 42.58 mmol, 60% purity, 1.5 eq) in batches. After stirring at 0°C for 30 min. TosCl (6.49 g, 34.07 mmol, 1.2 eq) was added in batches. The mixture was stirred at 0 °C for 30 min. TLC indicated reactant 4 was consumed completely. The reaction mixture was quenched with NH_4Cl solution (50 mL) at 25°C, diluted with water (20 mL), and then extracted with EtOAc (100 mL x 2). The combined organic layer waswashed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1) to afford 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (6.44 g, 17.03 mmol, 50.00% yield, 95% purity) as a brown solid. ^1H NMR was recorded.

Synthesis of methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



A mixture of 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2 g, 5.57 mmol, 1 eq) in THF (20 mL) was degassed and purged with N_2 for 3 times. LDA (2 M in THF, 4.18 mL, 1.5 eq) was then added. The reaction mixture was stirred at -60 °C for 10 min under N_2 atmosphere. To the mixture was then added methyl carbonochloridate (2.63 g, 27.84 mmol, 2.16 mL, 5 eq) and stirred at -60 °C for 30 min. TLC showed one major new spot. The reaction mixture was quenched by addition of saturated NH_4Cl solution (50 mL) at 25 °C, and then diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer waswashed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1) to afford methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.46 g, 2.80 mmol, 40.17% yield, 80% purity) as a yellow solid. ^{1}H NMR was recorded.

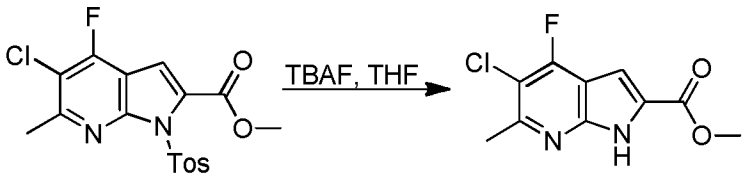
Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



To a mixture of methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.16 g, 2.78 mmol, 1 eq), methylboronic acid (216.35 mg, 3.61 mmol, 1.3 eq) and K_2CO_3 (768.48 mg, 5.56 mmol, 2 eq) was added DME (5 mL). The mixture was purged with N_2 and $Pd(dppf)Cl_2.CH_2Cl_2$ (227.04 mg, 278.02 umol, 0.1 eq) was then added under N_2. The

mixture was stirred at 100 °C for 12 hr. LC-MS showed desired mass. The mixture was filtered. The cake was washed with EtOAc (10 mL x 2). The combined filtrate was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (558 mg, 1.27 mmol, 45.52% yield, 90% purity) as a yellow solid. ^{1}H NMR was recorded.

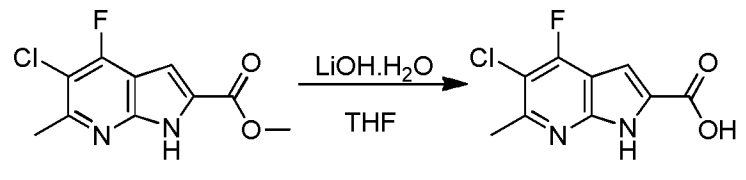
Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate



9 **10**

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (612 mg, 1.54 mmol, 1 eq) in THF (5 mL) was added TBAF (1 M in THF, 2.00 mL, 1.3 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated reactant 9 was consumed completely. The reaction mixture was concentrated under reduced pressure. The crude product was triturated with water (10 mL) at 25 °C for 30 min and filtered to afford methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (370 mg, crude) as a yellow solid. ^{1}H NMR was recorded.

Synthesis of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



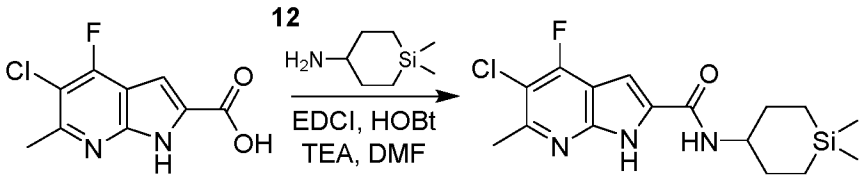
10 **11**

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (370 mg, 1.52 mmol, 1 eq) in THF (3 mL) was added a solution of LiOH.H_2O (383.92 mg, 9.15 mmol, 6 eq) in H_2O (3 mL), and stirring at 30 °C for 12 hr. TLC indicated reactant 10 was

consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. To the aqueous phase was added aqueous HCl (6 M) until pH to 2, filtered and concentrated under reduced pressure to give 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (330 mg, 1.37 mmol, 89.93% yield, 95% purity, crude) as a yellow solid. The crude product was used for the next step without further purification.

^{1}H NMR (500MHz, DMSO-d6) δ = 12.60 (br s, 1H), 6.97 (d, J=1.5 Hz, 1H), 2.53 - 2.46 (m, 3H)

Synthesis of 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



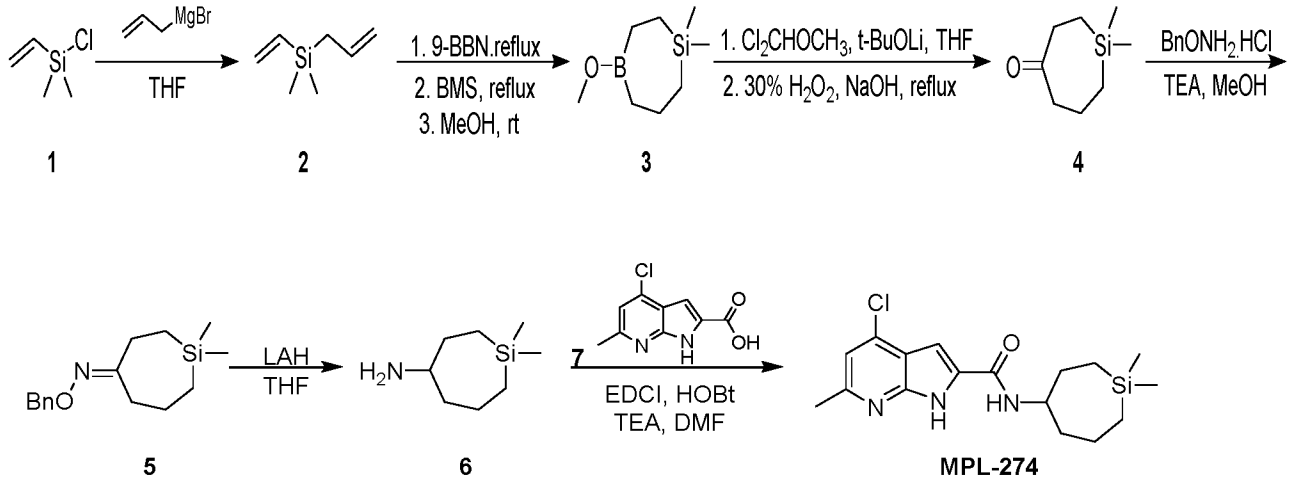
11 **MPL-232**

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (330 mg, 1.44 mmol, 1 eq) and 1,1-dimethylsilinan-4-amine (311.39 mg, 1.73 mmol, 1.2 eq, HCl) in DMF (3 mL) at 25 °C was added a solution of HOBt (585.16 mg, 4.33 mmol, 3 eq) and EDCI (830.18 mg, 4.33 mmol, 3 eq) in DMF (5 mL), followed by TEA (730.34 mg, 7.22 mmol, 1.00 mL, 5 eq). The mixture was stirred at 25 °C for 2 hr. LC-MS showed desired mass. The reaction mixture was quenched with aqueous $NaHCO_3$ ($NaHCO_3$: H_2O = 2:1) (100 mL) at 25 °C, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 3/1) to afford 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (230 mg, 639.83 umol, 44.32% yield, 98.45% purity) as a yellow solid.

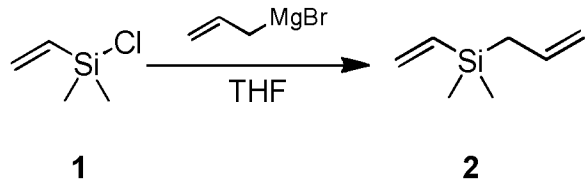
LCMS (ESI) m/z 354.0 $[M+H]^+$; ^{1}H NMR (500MHz, CHLOROFORM-d_3) δ = 9.69 (br s, 1H), 7.33 - 7.21 (m, 1H), 6.78 (d, J=2.1 Hz, 1H), 6.06 (br d, J=7.9 Hz, 1H), 4.02 - 3.83 (m, 1H), 2.72 (s, 3H), 2.19 (td, J=3.7, 9.3 Hz, 2H), 1.60 - 1.52 (m, 2H), 0.86 - 0.65 (m, 4H), 0.08 (d, J=18.8 Hz, 6H).

Example 136. MPL-274

Scheme

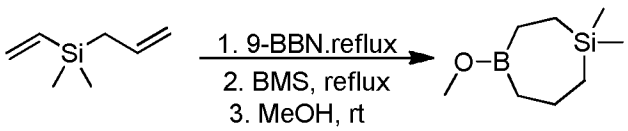


Synthesis of allyl-dimethyl-vinyl-silane



Chloro-dimethyl-vinyl-silane (30 g, 248.65 mmol, 1 *eq*) was added to allyl(bromo)magnesium (1 M, 497.30 mL, 2 *eq*) (in THF) at 30 °C under N_2. The mixture was stirred at 85 °C for 12 hr. TLC (petroleum ether) showed a new spot. The mixture was cooled to 0 °C, then poured to saturated NH_4Cl (600 mL), and extracted with n-pentane (200 mL). The organic layer was dried with Na_2SO_4 and filtered. The solvent was removed by distillation under 15 Psi at 110 °C. The prodcut was distilled under reduced pressure at 30 °C. Compound allyl-dimethyl-vinyl-silane (24 g, 142.55 mmol, 57.33% yield, 75% purity) was obtained as a colorless oil. ^1H NMR was recorded.

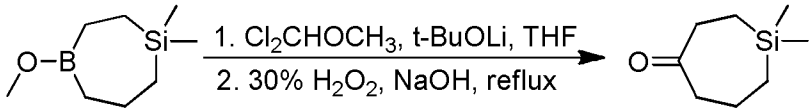
Synthesis of 4-methoxy-1,1-dimethyl-1,4-silaborepane



2 3

To a 1 L three necks flask purged with N_2 was added 9-BBN (0.5 M, 313.61 mL, 2.2 *eq*), followed by allyl-dimethyl-vinyl-silane (12 g, 71.28 mmol, 1 *eq*). The mixture was stirred at 80 °C under N2 for 3 hr. The mixture was cooled to 25 °C then BH_3-Me_2S (10 M, 8.55 mL, 1.2 *eq*) was added dropwise. The mixture was stirred at 80 °C for 2 hr. After cooled to 25 °C, MeOH (18.27 g, 570.20 mmol, 23.07 mL, 8 *eq*) was added dropwise, the mixture was stirred at 25 °C for additional 12 hr. TLC (petroleum ether : EtOAc = 10:1) showed two major spots. The solvents were removed by distillation at 120 °C (oil bath) under 15 Psi. Compound 4-methoxy-1,1-dimethyl-1,4-silaborepane (38 g, crude) was obtained as a light yellow oil.

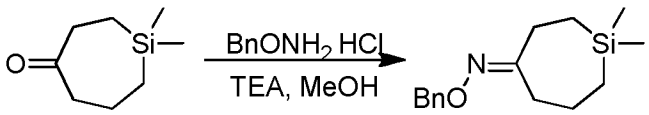
Synthesis of 1,1-dimethylsilepan-4-one



3 4

To a solution of 4-methoxy-1,1-dimethyl-1,4-silaborepane (38 g, 223.36 mmol, 1 *eq*) in t-BuOLi (2.2 M, 507.63 mL, 5 *eq*) was added dichloro(methoxy)methane (25.68 g, 223.36 mmol, 19.75 mL, 1 *eq*) dropwise at 0 °C with an ice-water bath. The mixture was stirred at 25 °C for 30 min. Then NaOH (26.80 g, 670.07 mmol, 3 *eq*) in a mixture of H_2O (32 mL) and EtOH (100 mL) was added, followed by dropwise addition of H_2O_2 (94.71 g, 835.35 mmol, 80.27 mL, 30% in H_2O, 3.74 *eq*). The solution was stirred at 90 °C for 3 hr. TLC (petroleum ether : EtOAc = 10:1) showed one major spot. The reaction was quenched by water (500 mL), then extracted with ethyl acetate (2 x 100 ml). The aqueous layer was quenched with sat. Na_2SO_3 (100 mL). The organic layers were combined and dried over Na_2SO_4, filtered and distilled at 120 °C (oil bath) under 15 Psi to remove the solvent. Compound 1,1-dimethylsilepan-4-one (44 g, crude) was obtained as a yellow oil. ^{1}H NMR was recorded.

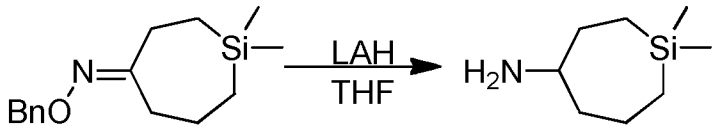
Synthesis of (E)-N-benzyloxy-1,1-dimethyl-silepan-4-imine



4 5

To an ice-cooled solution of 1,1-dimethylsilepan-4-one (43 g, 275.12 mmol, 1 *eq*) and TEA (55.68 g, 550.23 mmol, 76.59 mL, 2 *eq*) in MeOH (450 mL) was added O-benzylhydroxylamine (57.09 g, 357.65 mmol, 1.3 *eq*, HCl) at 0 °C. The mixture was stirred at 25 °C for 12 hr. TLC (petroleum ether : EtOAc = 50:1) showed one major spot under UV 254 nm and no spot stained by DNP (dinitrophenylhydrazine). The mixture was concentrated under reduced pressure to give a residue which was diluted with EtOAc (300 mL) and washed with water (200 mL) and brine (200 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated to give a residue which was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column; eluent of 0-3% ethyl acetate in petroleum ether at 100 mL/min). The fractions containing the product (checked by TLC; petroleum ether : EtOAc = 50:1) were collected and concentrated to give light yellow oil (18 g), which was further purified in two batches (8g and 10g) by prep-HPLC (column: Boston Uni C18 40*150*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 70%-100%, B over 11 min) to afford (E)-N-benzyloxy-1,1-dimethyl-silepan- 4-imine 5.0 g, 17.21 mmol, 6.25% yield, 90% purity) as a yellow oil. ^1H NMR was recorded.

Synthesis of 1,1-dimethylsilepan-4-amine



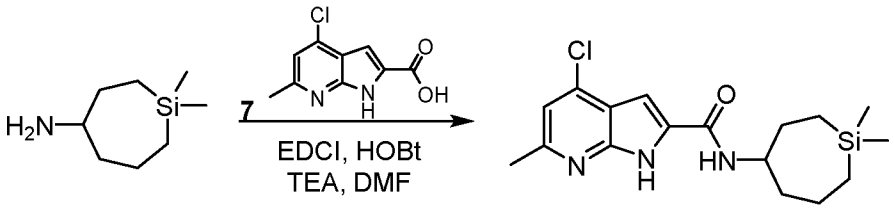
5 6

To an ice-cooled solution of (E)-N-benzyloxy-1,1-dimethyl-silepan-4-imine (0.5 g, 1.91 mmol, 1 *eq*) in THF (5 mL) was added LAH (145.16 mg, 3.83 mmol, 2 *eq*). The mixture was warmed to 25 °C and stirred for 1 hr, and then heated to 80 °C to reflux and stirred for 1.5 hr. TLC (petroleum ether : EtOAc = 1:1) showed starting material was consumed completely, and several new spots formed. The reaction was quenched with 0.15 mL of water and 0.15 mL of aq. NaOH

(15% in water), followed with 0.45 mL of water and Na_2SO_4, and then filtered. The cake was washed with MeOH/DCM (1:10, 5 mL x 3). The pH of combined filtrate was adjusted to 2 with HCl in MeOH, and the mixture was stirred at 25 °C for 2 hr and then concentrated under reduced pressure. The resulting residue was diluted with EtOAc (25 mL), and then extacted with water (7 mL x 4). The aqueous layers were combined, and then dried by lyophilizer to give 1,1-dimethylsilepan-4-amine (310 mg, 1.44 mmol, 75.28% yield, 90% purity, HCl salt) as a white solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.91 (br s, 3H), 3.02 (br s, 1H), 2.03 - 1.91 (m, 2H), 1.87 - 1.77 (m, 1H), 1.64 - 1.52 (m, 1H), 1.46 - 1.36 (m, 2H), 0.81 - 0.68 (m, 2H), 0.63 - 0.53 (m, 2H), 0.01 (d, J=9.8 Hz, 6H).

Synthesis of 4-chloro-N-(1,1-dimethylsilepan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



6 **MPL-274**

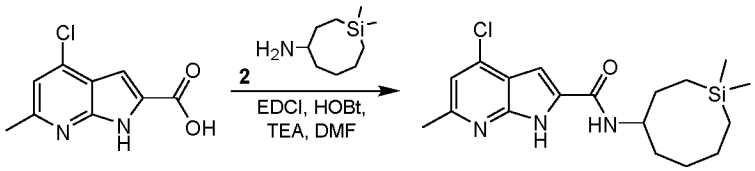
To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (550 mg, 2.61 mmol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (657.87 mg, 3.39 mmol, 1.3 *eq*, HCl) in DMF (7 mL) was added a solution of EDCI (1.00 g, 5.22 mmol, 2 *eq*) and HOBt (705.71 mg, 5.22 mmol, 2 *eq*) in DMF (7 mL), followed by TEA (1.06 g, 10.45 mmol, 1.45 mL, 4 *eq*). The mixture was stirred at 25 °C for 2 hrs. LC-MS showed the acid was consumed completely and one main peak with desired mass was detected. The mixture was poured into water, the crude product was isolated as red solid and collected by filtration. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, 0-15% ethyl acetate in petroleum ether at 40 mL/min). All fractions containing the desired product (checked by TLC (petroleum ether : EtOAc = 3:1) were combined and concentrated. The residue was dried by lyophilizer. Compound 4-chloro-N-(1,1-dimethylsilepan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (490 mg, 1.34 mmol, 51.44% yield, 95.929% purity) was obtained as

a light yellow solid.

LCMS (ESI) m/z 350.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.21 - 12.17 (m, 1H), 12.19 (br s, 1H), 8.33 - 8.21 (m, 1H), 8.30 (br d, J=8.1 Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 3.90 - 3.79 (m, 1H), 2.48 (s, 3H), 1.91 - 1.73 (m, 3H), 1.69 - 1.59 (m, 1H), 1.51 - 1.39 (m, 2H), 0.76 - 0.65 (m, 2H), 0.61 - 0.53 (m, 2H), -0.01 (d, J=9.3 Hz, 6H).

Example 137. MPL-275

Synthesis of 4-chloro-N-(1,1-dimethylsilocan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



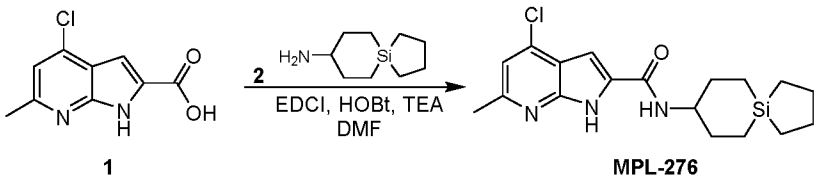
1 MPL-275

To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (25 mg, 118.70 umol, 1.2 *eq*) and 1,1-dimethylsilocan-4-amine (20.56 mg, 98.92 umol, 1 *eq*, HCl) in DMF (0.5 mL) was added a solution of EDCI (37.92 mg, 197.83 umol, 2 *eq*) and HOBt (26.73 mg, 197.83 umol, 2 *eq*) in DMF (0.5 mL), followed by TEA (40.04 mg, 395.66 umol, 55.07 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass was detected. The mixture was diluted with MeOH (2 mL) and filtered to remove insoluble matter. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 70%-100%B% over 11min). Compound 4-chloro-N-(1,1-dimethylsilocan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (20 mg, 54.95 umol, 55.55% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 364.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.24 (br s, 1H), 8.30 (d, J=7.9 Hz, 1H), 7.27 - 7.19 (m, 1H), 7.15 (s, 1H), 4.08 - 3.89 (m, 1H), 2.51 (s, 3H), 1.81 - 1.52 (m, 7H), 1.46 - 1.35 (m, 1H), 0.84 - 0.75 (m, 1H), 0.72 - 0.61 (m, 2H), 0.55 (ddd, J=3.0, 8.5, 15.2 Hz, 1H), 0.59 - 0.51 (m, 1H), 0.01 (d, J=11.9 Hz, 6H).

Example 138. MPL-276

Synthesis of 4-chloro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

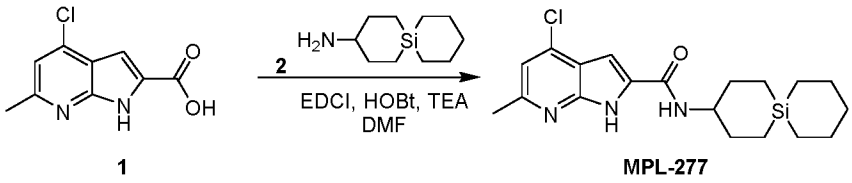


To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 237.40 umol, 1 *eq*) in DMF (1 mL) was added 5-silaspiro[4.5]decan-8-amine (53.74 mg, 261.14 umol, 1.1 *eq*. HCl salt). Then a solution of HOBt (64.16 mg, 474.80 umol, 2 *eq*) and EDCI (91.02 mg, 474.80 umol, 2 *eq*) in DMF (1 mL) was added to the mixture, followed by TEA (96.09 mg, 949.59 umol, 132.17 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hrs. LCMS showed one main peak with desired mass. DMF (3 mL) was added to the mixture, filtered to collect the filtrate which was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 65%-85%B over 11min). Compound 4-chloro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine- 2-carboxamide (61.5 mg, 169.92 umol, 71.57% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 362.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6): δ = 12.26 (s, 1 H) 8.33 (d, *J*=8.09 Hz, 1 H) 7.20 (s, 1 H) 7.17 (s, 1 H) 3.77 (td, *J*=11.02, 8.01 Hz, 1 H) 2.54 (s, 4 H) 2.04 - 2.12 (m, 2 H) 1.54 - 1.65 (m, 6 H) 0.72 - 0.87 (m, 4 H) 0.63 (br t, *J*=6.71 Hz, 2 H) 0.55 (br t, *J*=6.79 Hz, 2 H).

Example 139. MPL-277

Synthesis of 4-chloro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

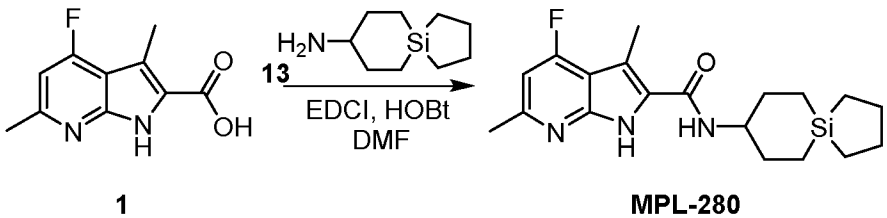


To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 237.40 umol, 1 *eq*) in DMF (1 mL) was added 6-silaspiro[5.5]undecan-3-amine (57.41 mg, 261.14 umol, 1.1 *eq*, HCl salt). Then a solution of HOBt (64.16 mg, 474.80 umol, 2 *eq*) and EDCI (91.02 mg, 474.80 umol, 2 *eq*) in DMF (1 mL) was added, and followed by TEA (96.09 mg, 949.60 umol, 132.17 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed one main peak with desired mass. DMF (3 mL) was added. The mixture was filtered. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 100*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; 75%-100%B over 11 min) to give desired compound 4-chloro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (68 mg, 180.87 umol, 76.19% yield, 100% purity) as a white solid.

LCMS (ESI) m/z 376.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.26 (s, 1 H) 8.33 (br d, *J*=7.93 Hz, 1 H) 7.19 (s, 1 H) 7.17 (s, 1 H) 3.67 - 3.80 (m, 1 H) 2.54 (s, 3 H) 2.01 (br d, *J*=9.92 Hz, 2 H) 1.53 - 1.74 (m, 6 H) 1.40 (br s, 2 H) 0.91 (br d, *J*=14.50 Hz, 2 H) 0.67 - 0.77 (m, 2 H) 0.56 - 0.66 (m, 4 H).

Example 140. MPL-280

Synthesis of 4-fluoro-3,6-dimethyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



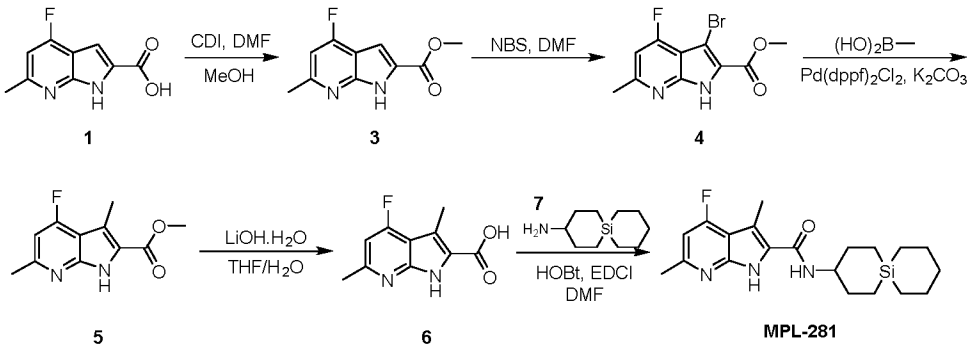
To a solution of 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 144.10 umol, 1 *eq*) and 5-silaspiro[4.5]decan-8-amine (35.59 mg, 172.92 umol, 1.2 *eq*, HCl salt)

in DMF (1 mL) was added a solution of EDCI (55.25 mg, 288.20 umol, 2 *eq*) and HOBt (38.94 mg, 288.20 umol, 2 *eq*) in DMF (1 mL), followed by TEA (58.33 mg, 576.40 umol, 80.23 uL, 4 *eq*). The mixture was stirred at 25 °C for 12 hr. LC-MS showed one main peak with desired mass. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 65%-95%B over 11min). Compound 4-fluoro-3,6-dimethyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (35 mg, 96.83 umol, 67.20% yield, 99.46% purity) was obtained as a white solid.

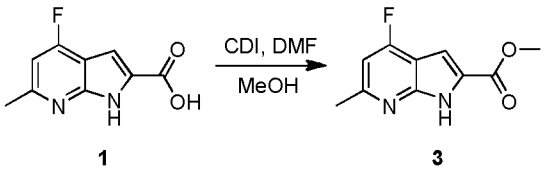
LCMS (ESI) m/z 360.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 11.86 (br s, 1H), 7.80 (br d, *J*=7.6 Hz, 1H), 6.83 (d, *J*=12.1 Hz, 1H), 3.82 - 3.71 (m, 1H), 2.57 (s, 3H), 2.53 - 2.52 (m, 3H), 2.09 (br d, *J*=10.4 Hz, 2H), 1.66 - 1.54 (m, 6H), 0.87 - 0.79 (m, 2H), 0.78 - 0.69 (m, 2H), 0.64 - 0.52 (m, 4H).

Example 141. MPL-281

Scheme



Synthesis of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2- carboxylate

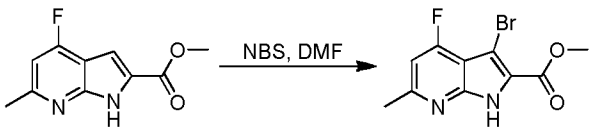


A solution of 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (3 g, 15.45 mmol, 1 *eq*) and CDI (2.76 g, 17.00 mmol, 1.1 *eq*) in DMF (30 mL) was stirred at 30 °C for 1 hr.

MeOH (23.75 g, 741.35 mmol, 30.00 mL, 47.98 *eq*) was then added and the reaction was stirred for 30 min. LCMS showed desired mass. The mixture was concentrated under reduced pressure to remove CH_3OH, and then poured into water (200 mL). The resulting suspension was filtered. The filter cake was collected, diluted with EtOAc (100 mL), dried over Na2SO4, filtered and concentrated under reduced pressure to give methyl 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2- carboxylate (1.6 g, 7.30 mmol, 40.74% yield, 95% purity) as a yellow solid.

LCMS (ESI) m/z 209.2$[M+H]^+$; ^1H NMR was recorded.

Synthesis of 3-bromo-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2- carboxylate

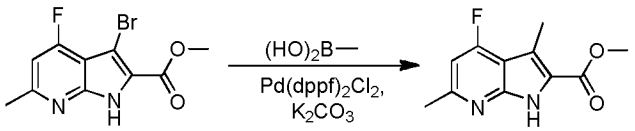


3 4

A solution of methyl 4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (1.5 g, 7.21 mmol, 1 *eq*) and NBS (1.41 g, 7.93 mmol, 1.1 *eq*) in DMF (30 mL) under N_2 was stirred at 30 °C for 3 hr. LCMS showed desired mass. The mixture was poured into water (200 mL). The suspension was filtered. The filter cake was washed with water (20 mL) and dried in vacuo to afford methyl 3-bromo-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2- carboxylate (1.2 g, 3.97 mmol, 55.11% yield, 95% purity) as a yellow solid.

LCMS (ESI) m/z 289.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 4-fluoro-3,6-dimethyl-1H- pyrrolo[2,3-b]pyridine-2-carboxylate



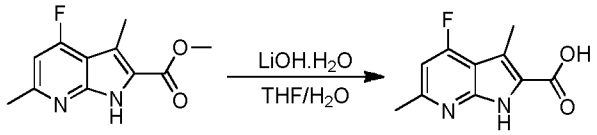
4 5

To a mixture of methyl 3-bromo-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (600 mg, 2.09 mmol, 1 *eq*), methylboronic acid (625.54 mg, 10.45 mmol, 5 *eq*) and Cs_2CO_3 (2.04 g, 6.27 mmol, 3 *eq*) in dioxane (10 mL) and H_2O (0.1 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$

(170.68 mg, 209.00 umol, 0.1 *eq*) under N_2. The reaction mixture was stirred at 110 °C for 12 hr. LCMS showed desire mass. The mixture was filtered. The filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleumn ether/ethyl aceate = 50/1 to 1/1) to afford methyl 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (110 mg, 346.51 umol, 16.58% yield, 70% purity) as a white solid.

LCMS (ESI) m/z 223.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

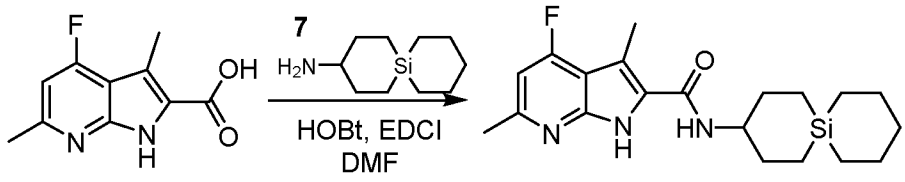


5 **6**

To a solution of methyl 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (362 mg, 1.63 mmol, 1 *eq*) in THF (5 mL) was added a solution of $LiOH.H_2O$ (410.17 mg, 9.77 mmol, 6 *eq*) in H_2O (5 mL). The mixture was stirred at 30 °C for 2 hr.LCMS showed desired mass. The mixture was concentrated under reduced pressure to remove THF. The aqueous solution was adjusted to pH to 4 with aq. HCl (6M). The suspension was filtered, and the filter cake was washed with water (10 mL) and collected. Compound 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (339 mg, crude) was obtained as a white solid.

LCMS (ESI) m/z 209.1$[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4-fluoro-3,6-dimethyl-N-(6-silaspiro[5.5]undecan-3-yl)- 1H-pyrrolo[2,3-b]pyridine-2-carboxamide



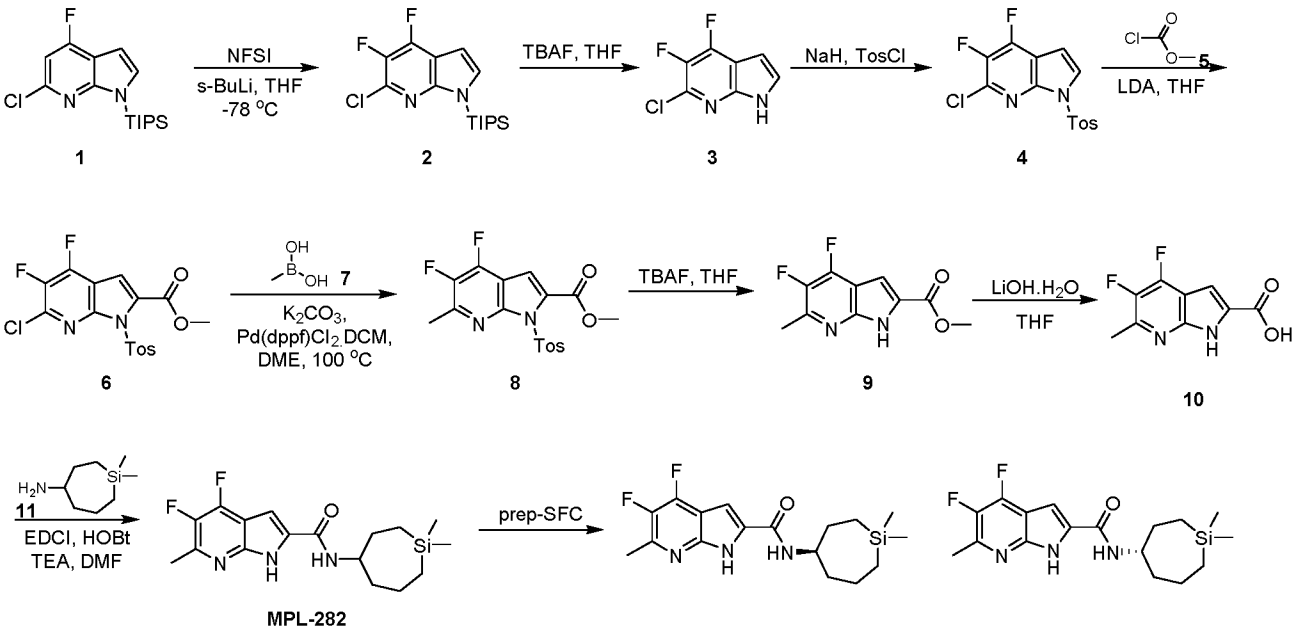
6 **MPL-281**

To a solution of 4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (289 mg, 1.39 mmol, 1 *eq*) and 6-silaspiro[5.5]undecan-3-amine (335.67 mg, 1.53 mmol, 1.1 *eq*, HCl) in DMF (3 mL) was added a solution of EDCI (798.34 mg, 4.16 mmol, 3 *eq*) and HOBt (562.72 mg, 4.16 mmol, 3 *eq*) in DMF (2 mL), followed by TEA (702.33 mg, 6.94 mmol, 966.07 uL, 5 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed desired mass. The mixture was filtered, and the filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 75%-100%B over13 min) to afford 4-fluoro-3,6-dimethyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (166.5 mg, 427.33 umol, 30.78% yield, 95.87% purity) as a white solid.

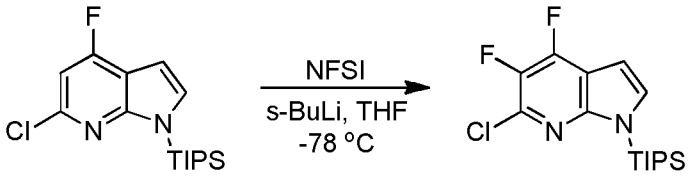
LCMS (ESI) m/z 274.1[M+H]$^+$; ^{1}H NMR (500 MHz, DMSO-*d*6) δ = 0.51 - 0.65 (m, 4 H) 0.65 - 0.73 (m, 2 H) 0.82 - 0.95 (m, 2 H) 1.39 (br s, 2 H) 1.51 - 1.73 (m, 6 H) 1.94 - 2.09 (m, 2 H)2.52 (br s, 3 H) 2.54 - 2.60 (m, 3 H) 3.65 - 3.82 (m, 1 H) 6.82 (d, *J*=12.05 Hz, 1 H) 7.79 (br d, *J*=7.63 Hz, 1 H) 11.88 (br s, 1 H).

Example 142. MPL-282, MPL-282A and MPL-282B

Scheme



Synthesis of (6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane

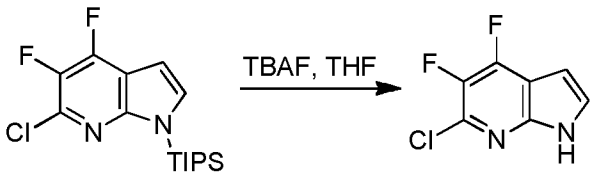


1 **2**

To a solution of (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (10 g, 30.59 mmol, 1 eq) in THF (100 mL) was added a solution of s-BuLi (1.3 M in n-hexane, 44.71 mL, 1.9 eq). The mixture was stirred at -78 °C for 0.5 hr. Then a solution of NFSI (28.94 g, 91.77 mmol, 3 eq) in THF (100 mL) was added. The reaction mixture was stirred at -78 °C for 1.5 hr. LC-MS showed desired mass. The reaction mixture was quenched by addition of saturated NH_4Cl (100 mL) at -78°C, and then extracted with EtOAc (200 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1) to afford (6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9 g, 23.48 mmol, 76.77% yield, 90% purity) as a yellow oil.

LCMS (ESI) m/z 345.2 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine

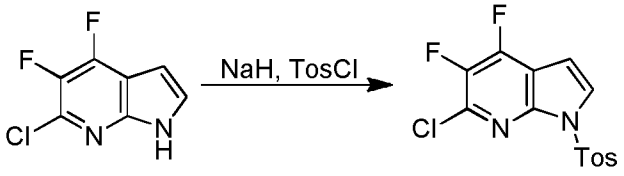


2 **3**

To a solution of (6-chloro-4,5-difluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9 g, 26.09 mmol, 1 eq) in THF (50 mL) was added TBAF (1 M in THF, 39.14 mL, 1.5 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with water (100 mL) for 20 min, filtered, and the filter cake was washed with petroleum ether (20 mL x 3). The cake

was dried under reduced pressure. Compound 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine (3.2 g, 15.27 mmol, 58.53% yield, 90% purity) was obtained as a yellow solid. ^{1}H NMR was recorded. The crude product was used for the next step without purification.

Synthesis of 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

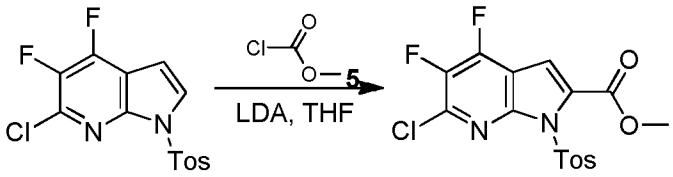


3 4

To a solution of 6-chloro-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine (5.3 g, 28.11 mmol, 1 eq) in THF (50 mL) was added NaH (3.37 g, 84.32 mmol, 60% purity, 3 eq) at 0 °C under N_2, followed by the solution of TosCl (8.04 g, 42.16 mmol, 1.5 eq) in THF (30 mL) dropwise at 0 °C. The reaction mixture was then stirred at 0 °C for 0.5 hr. LC-MS showed desired compound was detected.The reaction mixture was poured into saturated NH_4Cl (100 mL), and then extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/tthyl acetate = 1/0 to 10/1) to afford 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (7.7 g, 22.47 mmol, 79.93% yield) as a yellow solid.

LCMS (ESI) m/z 343.0 $[M+H]^+$; ^{1}H NMR was recorded.

Synthesis of methyl 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

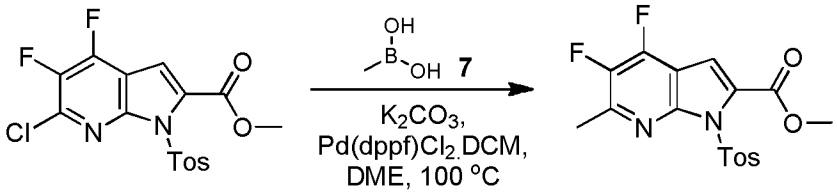


4 6

A mixture of 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (6.7 g, 19.55 mmol, 1 eq) in THF (70 mL) was degassed and purged with N_2 for 3 times. LDA (2 M in THF, 14.66 mL, 1.5 eq) and stirred at -78 °C for 10 min under N_2 atmosphere. Methyl carbonochloridate (9.24 g, 97.74 mmol, 7.57 mL, 5 eq) was then added. The mixture was stirred at -78 °C for 30 min. LC-MS showed desire mass. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) at 25 °C, and then diluted with water (50 mL), and extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford methyl 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (3.1 g, 6.19 mmol, 31.65% yield, 80% purity) as a yellow solid.

LCMS (ESI) m/z 401.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

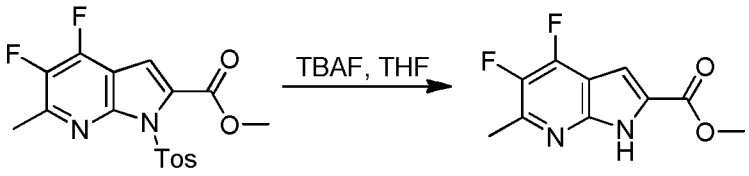


6 **8**

To a mixture of methyl 6-chloro-4,5-difluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (3.1 g, 7.73 mmol, 1 eq) in DME (30 mL) was added methylboronic acid (2.32 g, 38.67 mmol, 5 eq) and K_2CO_3 (3.21 g, 23.20 mmol, 3 eq). The mixture was purged with N_2 and $Pd(dppf)Cl_2.CH_2Cl_2$ (631.66 mg, 773.48 umol, 0.1 eq) was added under N_2. The mixture was stirred at 100 °C for 12 hr. LC-MS showed desired mass. The reaction mixture was filtered, the cake was washed with EtOAc (10 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford methyl 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (800 mg, 2.00 mmol, 25.83% yield, 95% purity) as a yellow solid.

LCMS (ESI) m/z 381.0 $[M+H]^+$; ^1H NMR was recorded.

Step 6. Synthesis of methyl 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate

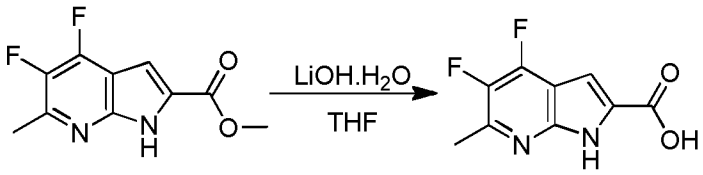


8 **9**

To a solution of methyl 4,5-difluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1 g, 2.63 mmol, 1 eq) in THF (5 mL) was added TBAF (1 M in THF, 3.94 mL, 1.5 eq).The mixture was stirred at 25 °C for 0.5 hr. TLC indicated the reactant was consumed completely. The reaction mixture was concentrated under reduced pressure. The resulting residue was triturated with water (20 mL) for 20 min and filtered. The cake was collected, washed with petroleum ether (10 mL x 3), concentrated under reduced pressure. Compound methyl 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (620 mg, 2.19 mmol, 83.41% yield, 80% purity) was obtained as a yellow solid. The crude product was used for the next step without further purification.

LCMS (ESI) m/z 227.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



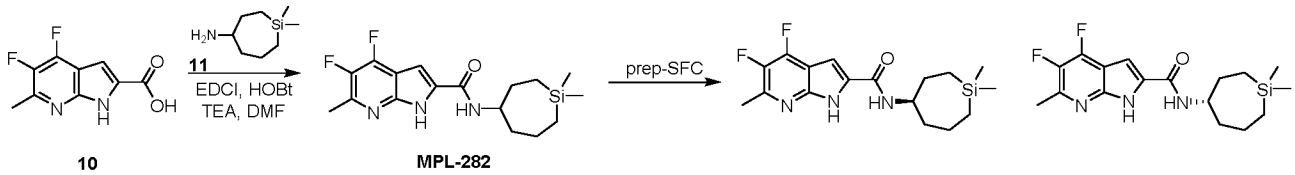
9 **10**

To a solution of methyl 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (620 mg, 2.74 mmol, 1 eq) in THF (3 mL) and H_2O (3 mL) was added $LiOH.H_2O$ (575.15 mg, 13.71 mmol, 5 eq). The mixture was stirred at 25 °C for 12 hr. LC-MS showed the desired product was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with water (10 mL), aq. HCl (6M) was added until pH to 2. The mixture was

filtered and concentrated in vacuo.Compound 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (500 mg, 2.12 mmol, 77.38% yield, 90% purity) was obtained as a yellow solid, which was used for the next step without further purification.

LCMS (ESI) m/z 212.8 $[M+H]^+$; 1H NMR (500MHz, DMSO-d6) δ = 13.38 (br s, 1H), 12.64 (br s, 1H), 7.14 (d, *J*=2.0 Hz, 1H), 2.55 (d, *J*=3.5 Hz, 3H).

Synthesis of N-(1,1-dimethylsilepan-4-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide, N-[(4R)-1,1-dimethylsilepan-4-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide **and** ***N-[(4S)-1,1-dimethylsilepan-4-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide***



To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 eq) and 1,1-dimethylsilepan-4-amine (43.85 mg, 226.25 umol, 1.2 eq, HCl) in DMF (1 mL) at 25 °C was added a solution of HOBt (76.43 mg, 565.63 umol, 3 eq) and EDCI (108.43 mg, 565.63 umol, 3 eq) in DMF (1 mL), followed by TEA (95.39 mg, 942.72 umol, 131.21 uL, 5 eq), and the mixture was stirred at 25 °C for 1 hr. LC-MS showed desired compound was detected. The reaction mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 66%-95%B over 11 min). Compound N-(1,1-dimethylsilepan-4-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (29.7 mg, 82.95 umol, 43.99% yield, 98.16% purity) was obtained as a white solid.

LCMS (ESI) m/z 352.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d6) δ = 12.37 (br s, 1H), 8.32 (br d, *J*=7.8 Hz, 1H), 7.24 (s, 1H), 3.88 (br s, 1H), 2.53 (d, *J*=3.5 Hz, 3H), 1.92 - 1.47 (m, 6H), 0.81-0.57 (m, 4H), 0.04 (d, *J*=7.0 Hz, 6H).

The same reaction was conducted at 707.04 umol scale. The reaction mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 60%-90% B over 11min). The residue was further purified by SFC (Sepiatec Prep SFC 100, column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: A: 0.1% NH_3H_2O in MeOH,B CO_2, isocratic 60%B; Flow rate: 80 mL/min) to afford two peaks (two enantiomers), N-[(4R)-1,1-dimethylsilepan-4-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide and N-[(4S)-1,1-dimethylsilepan-4-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide.

Peak1 (MPL-282A): 51.7 mg, 147.10 umol, 20.80% yield, 100% purity, white solid.

LCMS (ESI) m/z 352.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.36 (br s, 1H), 8.32 (d, *J*=7.9 Hz, 1H), 7.24 (s, 1H), 4.00 - 3.78 (m, 1H), 2.53 (d, *J*=3.4 Hz, 3H) , 1.96 - 1.43 (m, 6H), 0.85 - 0.54 (m, 4H), 0.04 (d, *J*=8.9 Hz, 6H).

Peak 2 (MPL-282B): 50.2 mg, 142.83 umol, 20.20% yield, 100% purity, white solid. LCMS (ESI) m/z 352.3 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.35 (br s, 1H), 8.32 (d, *J*=7.9 Hz, 1H), 7.24 (s, 1H), 3.96 - 3.81 (m, 1H), 2.53 (d, *J*=3.5 Hz, 3H), 2.00 - 1.37 (m, 6H), 0.83 - 0.55 (m, 4H), 0.04 (d, *J*=8.9 Hz, 6H).

MPL-282A and MPL-282B were also analyzed by analytical SFC.

Conditions:

Instrument: CAS-SH-ANA-SFC-K (Waters UPCC with PDA Detector)

Column: Chiralpak AD-3 50*4.6mm, 3um particle size

Mobile phase: A: CO_2; B: 0.05% DEA in MeOH

Isocratic: 40% B

Flow rate: 4 mL/min

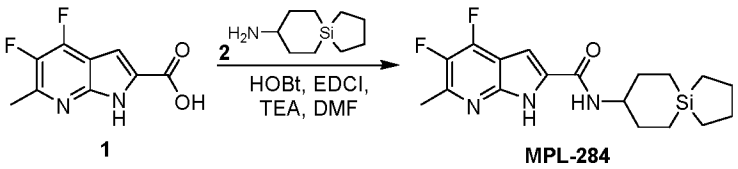
Column temp: 35°C

ABPR: 1500 psi

MPL-282A: retention time 1.22 min; 100% ee; MPL-282B: retention time 1.93 min; 100% ee

Example 143. MPL-284

Synthesis of 4,5-difluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

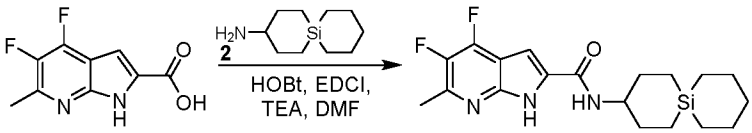


To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 235.68 umol, 1 *eq*) and 5-silaspiro[4.5]decan-8-amine (50 mg, 242.95 umol, 1.03 *eq*, HCl salt) in DMF (5 mL) was added HOBt (95.54 mg, 707.04 umol, 3 *eq*) and EDCI (135.54 mg, 707.04 umol, 3 *eq*), followed by TEA (143.09 mg, 1.41 mmol, 196.82 uL, 6 *eq*). The mixture was stirred at 30 °C for 1 hr. LC-MS indicated desired product was detected. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with saturated $NaHCO_3$ (30 mL x 2) and 5% LiCl in water (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150 x 30mmx4um; mobile phase: 0.05% HCl in water, B: CH3CN, gradient:70%-90% over 9 min) to afford 4,5-difluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H- pyrrolo[2,3-b]pyridine-2-carboxamide (19.6 mg, 53.11 umol, 22.54% yield, 98.5% purity) as a white solid.

LCMS m/z: 364.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.14 (s, 1H), 3.81 (br t, *J*=11.3 Hz, 1H), 2.57 (d, *J*=3.5 Hz, 3H), 2.20 (br d, *J*=11.0 Hz, 2H), 1.72 - 1.54 (m, 6H), 0.91 - 0.80 (m, 4H), 0.67 (br t, *J*=6.7 Hz, 2H), 0.58 (br t, *J*=6.8 Hz, 2H).

Example 144. MPL-285

Synthesis of 4,5-difluoro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide

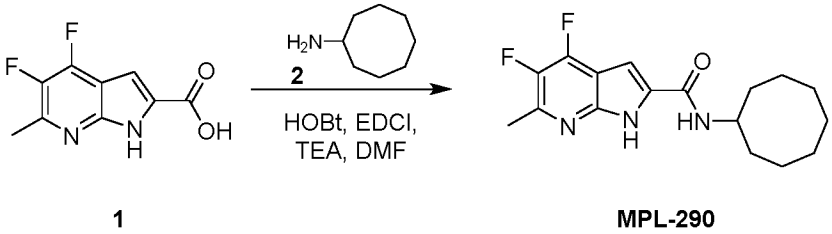


To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 235.68 umol, 1 *eq*) and 6-silaspiro[5.5]undecan-3-amine (51.81 mg, 235.68 umol, 1 *eq*. HCl salt) in DMF (5 mL) was added HOBt (95.54 mg, 707.04 umol, 3 *eq*) and EDCI (135.54 mg, 707.04 umol, 3 *eq*) , followed by TEA (143.09 mg, 1.41 mmol, 196.82 uL, 6 *eq*). The mixture was stirred at 30 °C for 1 hr. LC-MS indicated desired product was detected.The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc 90 mL (30 mL x 3). The combined organic layer was washed with saturated $NaHCO_3$ (30 mL x 2) and 5% LiCl in water (30 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, eluent of 0-10% ethyl acetate in petroleum ether at 30 mL/min) to afford 4,5-difluoro-6-methyl-N- (6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (27.1 mg, 71.57 umol, 30.37% yield, 99.692% purity) as a white solid.

LCMS m/z: 378.1 $[M+H]^+$; ^{1}H NMR (400 MHz, METHANOL-d_4) δ = 7.14 (s, 1H), 3.78 (br t, *J*=11.3 Hz, 1H), 2.57 (d, *J*=3.5 Hz, 3H), 2.13 (br d, *J*=9.4 Hz, 2H), 1.80 - 1.59 (m, 6H), 1.45 (brd, *J*=5.1 Hz, 2H), 0.96 (br d, *J*=14.5 Hz, 2H), 0.82 - 0.73 (m, 2H), 0.71 - 0.61 (m, 4H).

Example 145. MPL-290

Synthesis of N-cyclooctyl-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



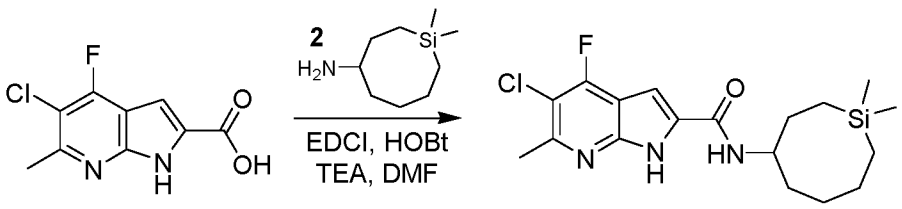
To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 eq) and cyclooctanamine (23.99 mg, 188.54 umol, 1 eq) in DMF (0.5 mL) was

added a solution of HOBt (76.43 mg, 565.63 umol, 3 eq) and EDCI (108.43 mg, 565.63 umol, 3 eq) in DMF (0.5 mL), followed by TEA (114.47 mg, 1.13 mmol, 157.46 uL, 6 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed that desired compound was detected. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 55%-85% B over 11min). Compound N-cyclooctyl-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (20 mg, 61.70 umol, 32.72% yield, 99.14% purity) was obtained as a white solid.

LCMS m/z: 322.2 $[M+1]^+$; ^1H NMR (400MHz, METHANOL-*d*4) δ = 7.17 (s, 1H), 4.20 - 4.12 (m, 1H), 2.58 (d, J=3.5 Hz, 3H), 1.93 - 1.85 (m, 2H), 1.83 - 1.74 (m, 4H), 1.71 - 1.59 (m, 8H).

Example 146: MPL-292

Syntheis of 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



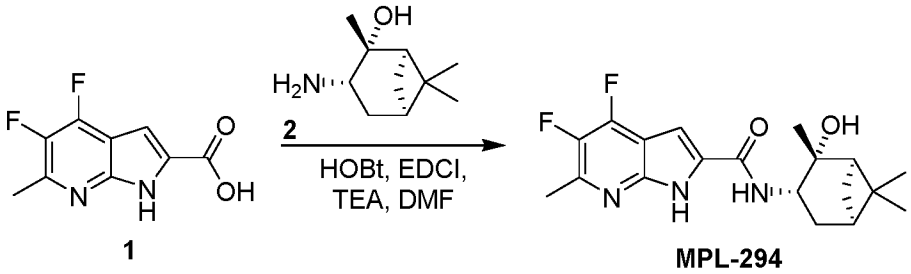
1 **MPL-292**

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 131.23 umol, 1 eq) and 1,1-dimethylsilocan-4-amine (30.00 mg, 144.35 umol, 1.1 eq, HCl salt) in DMF (1 mL) at 25 °C was added a solution of EDCI (75.47 mg, 393.69 umol, 3 eq) and HOBt (53.20 mg, 393.69 umol, 3 eq) in DMF (1 mL), followed by TEA (66.40 mg, 656.15 umol, 91.33 uL, 5 eq). The reaction mixture was stirred at 25 °C for 2 hrs. LC-MS showed desired compound was detected. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 75%-100%B over11 min). Compound 5-chloro-N-(1,1-dimethylsilocan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (18.7 mg, 45.71 umol, 34.83% yield, 93.361% purity) was obtained as a white solid.

LCMS (ESI) m/z 382.1 $[M+H]^+$; ^1H NMR (500MHz, CHLOROFORM-d) δ = 9.41 (br s, 1H), 6.78 (d, J=2.0 Hz, 1H), 6.08 (br d, J=7.8 Hz, 1H), 4.26 - 4.05 (m, 1H), 2.72 (s, 3H), 2.11 - 1.97 (m, 1H), 1.78 - 1.64 (m, 5H), 1.64 - 1.58 (m, 2H), 0.88 - 0.58 (m, 4H), 0.12 - 0.02 (m, 6H).

Example 147. MPL-294

Synthesis of 4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]- 6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

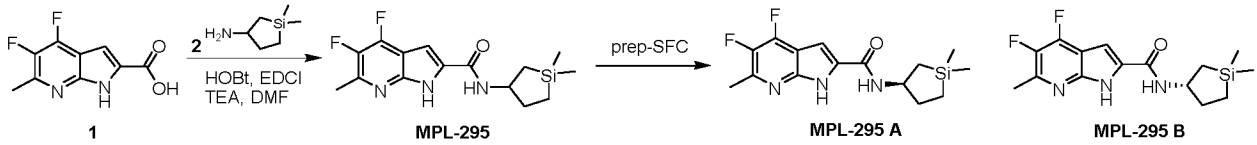


To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 235.68 umol, 1 *eq*) and (1R,2R,3S,5R)-3-amino-2,6,6-trimethyl-norpinan-2-ol (50 mg, 243.04 umol, 1.03 *eq*, HCl) in DMF (2 mL) was added HOBt (95.53 mg, 707.04 umol, 3 *eq*) and EDCI (135.54 mg, 707.04 umol, 3 *eq*), followed by TEA (143.09 mg, 1.41 mmol, 196.82 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150 x 30mm x 4um; mobile phase A: 0.05% HCl in water, B: CH3CN, gradient: 65%-85% B over 9 min) to afford a white solid (50mg), which was further purified by prep-SFC (column: DAICEL CHIRALPAK AD-H(250mm x 30mm,5um); mobile phase: A: 0.1% NH_3H_2O in IPA, B: CO_2; isocratic 25%B, flow rate: 80mL/min) and followed by lyophilization to give the desired compound 4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (16 mg, 44.03 umol, 32.00% yield, 100% purity) as a white solid.

LCMS m/z: 364.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.27 - 7.15 (m, 1H), 4.70 - 4.60 (m, 1H), 2.61 (d, J=3.5 Hz, 3H), 2.55 - 2.46 (m, 1H), 2.32 - 2.23 (m, 1H), 2.08 -2.02 (m, 1H), 2.01 - 1.96 (m, 1H), 1.73 (ddd, J=1.8, 7.5, 13.6 Hz, 1H), 1.66 (d, J=10.4 Hz, 1H), 1.35 (d, J=7.8 Hz, 6H), 1.16 (s, 3H).

Example 148. MPL-295, MPL-295A and MPL-295B

Synthesis of N-(1,1-dimethylsilolan-3-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide, N-[(3R)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide and N-[(3S)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 141.41 umol, 1 *eq*) and 1,1-dimethylsilolan-3-amine (23.44 mg, 141.41 umol, 1 *eq*, HCl salt) in DMF (2 mL) was added HOBt (57.32 mg, 424.22 umol, 3 *eq*) and EDCI (81.32 mg, 424.22 umol, 3 *eq*), followed by TEA (85.85 mg, 848.45 umol, 118.09 uL, 6 *eq*). The mixture was stirred at 25 °C for 2 hr. LC-MS indicated desired compound was detected. MeOH (0.5 mL) was added and the mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150 x 30mm x 4um; mobile phase: A: 0.05%HCl in water, B: CH_3CN; gradient: 60%-80%B over 9 min). Compound N-(1,1-dimethylsilolan- 3-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (17.6 mg, 53.19 umol, 37.62% yield, 97.743% purity) was obtained as a white solid.

LCMS m/z: 324.1 $[M+H]^+$; ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.00 (s, 1H), 3.97 - 3.82 (m, 1H), 2.41 (d, *J*=3.4 Hz, 3H), 2.08 - 1.88 (m, 1H), 1.29 (dq, *J*=7.2, 12.2 Hz, 1H), 1.10 -0.99 (m, 1H), 0.69 (dd, *J*=6.5, 14.3 Hz, 1H), 0.51 - 0.35 (m, 2H), 0.00 (d, *J*=1.7 Hz, 6H).

The above reaction was later conducted at 471.36 umol. The product isolated from prep-HPLC (column: Phenomenex Synergi C18 100*21.2mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 52%-82%B over 11 min) was further by SFC (Berger MG II, column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: A: 0.1%NH_3H_2O in EtOH; B: CO_2; isocratic 50%B; flow rate: 80 mL/min) to give two peaks (two enantiomers), N-[(3R)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

and N-[(3S)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide.

Peak 1 (MPL-295A): 33.4 mg, 103.27 umol, 21.91% yield, 100% purity.

LCMS (ESI) m/z 324.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.36 (br s, 1H), 8.35 (d, *J*=7.6 Hz, 1H), 7.22 (s, 1H), 4.02 (dq, *J*=7.0, 11.5 Hz, 1H), 2.53 (d, *J*=3.4 Hz, 3H), 2.10 - 1.97 (m, 1H), 1.44 (dq, *J*=7.2, 12.0 Hz, 1H), 1.17 - 1.06 (m, 1H), 0.81 (ddd, *J*=1.8, 7.1, 14.6 Hz, 1H), 0.69 - 0.46 (m, 2H), 0.18 (d, *J*=2.7 Hz, 6H).

Peak 2 (MLL-295B): 32.5 mg, 100.49 umol, 21.32% yield, 100% purity.

LCMS (ESI) m/z 324.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.36 (br s, 1H), 8.35 (d, *J*=7.6 Hz, 1H), 7.22 (s, 1H), 4.08 - 3.94 (m, 1H), 2.53 (d, *J*=3.4 Hz, 3H), 2.08 - 2.00 (m, 1H), 1.50 - 1.38 (m, 1H), 1.17 - 1.06 (m, 1H), 0.86 - 0.77 (m, 1H), 0.68 - 0.48 (m, 2H), 0.18 (d, *J*=2.7 Hz, 6H).

MPL-295A and MPL-295B was also analyzed by analytical SFC.

Conditions:

Instrument: CAS-SH-ANA-SFC-L (Waters UPCC with PDA Detector)

Column: Chiralpak AD-3 150mm*4.6mm, 3um particle size

Mobile phase: A: CO_2, B: 0.05% DEA in ethanol

Gradient: 5% to 40% of B in 5 min and hold 40%B for 2.5 min, then 5% of B for 2.5 min

Flow rate: 2.5mL/min

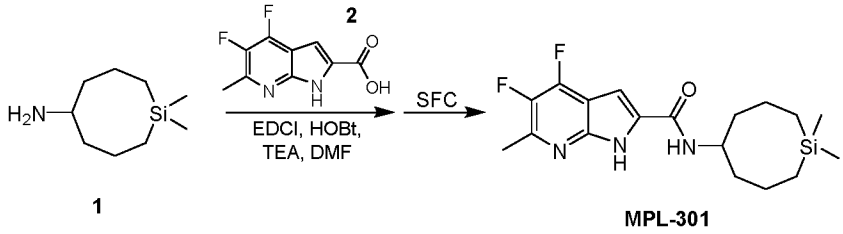
Column temp.: 35 °C

ABPR: 1500 psi

MPL-295A: retention time: 6.19 min; 100% ee; MPL-295B: retention time: 7.250 min, 100% ee

Example 149. MPL-301

Synthesis of N-(1,1-dimethylsilocan-5-yl)-4,5-difluoro-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide



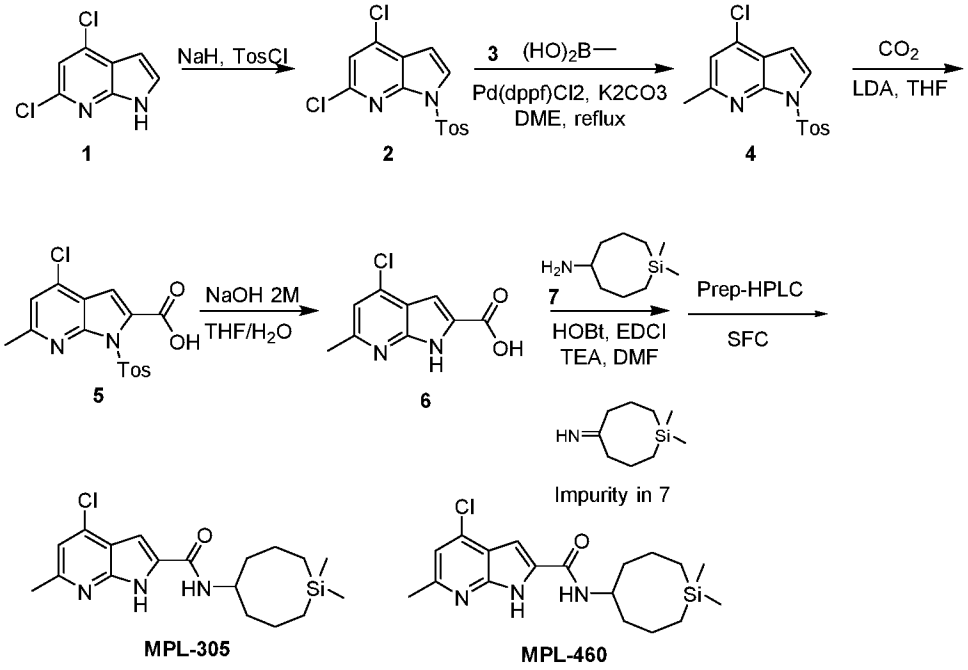
1 MPL-301

To a solution of 4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 188.54 umol, 1 *eq*) and 1,1-dimethylsilocan-5-amine (35.26 mg, 169.69 umol, 0.9 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (72.29 mg, 377.09 umol, 2 *eq*) and HOBt (50.95 mg, 377.09 umol, 2 *eq*) in DMF (0.5 mL), followed by TEA (76.31 mg, 754.17 umol, 104.97 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed one main peak with desired mass. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A 0.225% formic acid in water, B: CH_3CN; gradient: 70%-100%B over 11min). The resulting residue was further purified by SFC (Berger MG II, column: DAICEL CHIRALPAK AD (250mm*30mm,10um); mobile phase column: 0.1%NH_3H_2O in EtOH, B: CO_2; isocratic 40%B, flow rate 80 mL/min). Compound N-(1,1-dimethylsilocan-5-yl) -4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (28.2 mg, 76.76 umol, 40.71% yield, 99.49% purity) was obtained as a white solid.

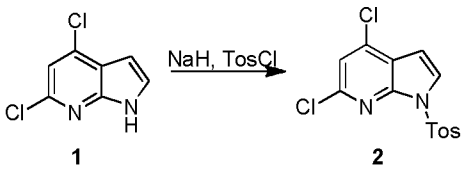
LCMS (ESI) m/z 366.1 $[M+H]^+$; ^1H NMR (500MHz, Acetone-*d*6) = 11.18 (br s, 1H), 7.75 (br d, *J*=7.2 Hz, 1H), 7.25 - 6.99 (m, 1H), 4.42 - 3.97 (m, 1H), 2.55 (d, *J*=3.5 Hz, 3H), 1.83 - 1.65 (m, 8H), 0.80 (t, *J*=6.2 Hz, 4H), 0.11 - -0.03 (m, 6H).

Example 150. MPL-305 and MPL-460

Scheme

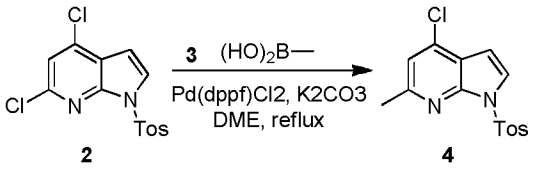


Synthesis of 4,6-dichloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 4,6-dichloro-1H-pyrrolo[2,3-b]pyridine (5 g, 26.73 mmol, 1 *eq*) in THF (100 mL) was added NaH (1.60 g, 40.10 mmol, 60% purity, 1.5 *eq*) in batches at 0 °C. The mixture was stirred at 0 °C for 1 hr. 4-methylbenzenesulfonyl chloride (6.12 g, 32.08 mmol, 1.2 *eq*) was added at 0 °C. The reaction mixture was stirred at 15 °C for 1 hr. TLC (petroleum ether : EtOAc = 10:1) showed starting material was consumed completely, and one major spot formed. The mixture was poured into saturated NH_4Cl (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (50 mL x 2), fitlered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, eluent of 0~30% ethyl acetate in petroleum ether at 40 mL/min). Compound 4,6-dichloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (7.5 g, 21.54 mmol, 80.57% yield, 98% purity) was obtained as a white solid. ^1H NMR was recorded.

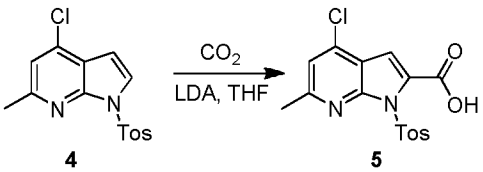
Synthesis of 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



2 4

To a mixture of 4,6-dichloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (7 g, 20.52 mmol, 1 *eq*), methylboronic acid (1.72 g, 28.72 mmol, 1.4 *eq*) and K_2CO_3 (8.51 g, 61.55 mmol, 3 *eq*) in DME (300 mL) was added $Pd(dppf)Cl_2.CH_2Cl_2$ (1.68 g, 2.05 mmol, 0.1 *eq*) under N_2. The mixture was stirred and refluxed at 120 °C (outside temperature) for 12 hr. TLC (petroleum ether : EtOAc = 10:1) showed starting material was consumed completely and two major spots formed. The mixture was filtered, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~5% ethyl acetate in petroleum ether at 85 mL/min). Compound 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (4.3 g, 12.73 mmol, 62.07% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

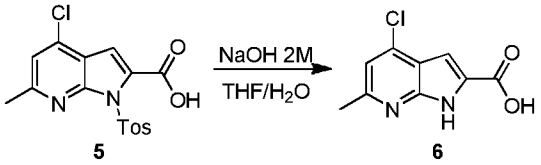
Synthesis of 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid



4 5

To a solution of 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (0.5 g, 1.56 mmol, 1 *eq*) in THF (10 mL) (dried by Na, and distilled) was added LDA (2 M in THF, 1.17 mL, 1.5 *eq*) under N_2 at -78 °C dropwise. The mixture was stirred at -78 °C for 1.5 hr. The reaction mixture was then purged with CO_2 for 3 times, and was allowed to warm to 10 °C gradually and stirred under CO_2 for 2 hr. LC-MS showed one main peak with desired mass. Compound 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (568 mg, crude) was obtained as a white solid suspended in THF..

Synthesis of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

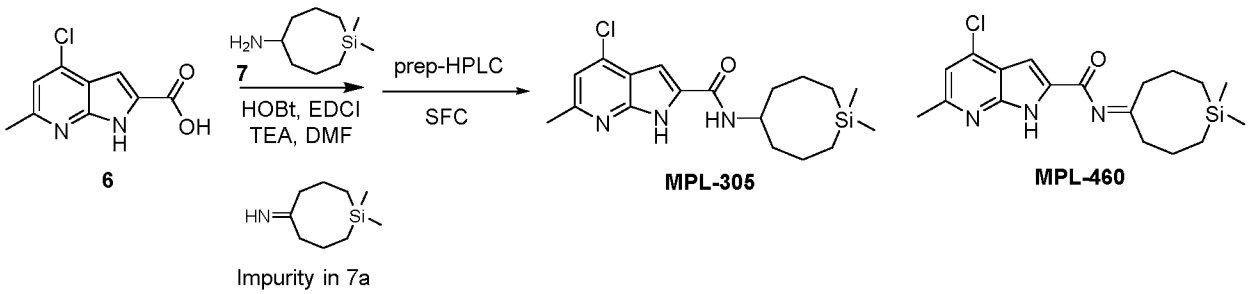


5 6

To a solution of 4-chloro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylic acid (568 mg, crude, 1.56 mmol, 1 *eq*) in THF was added NaOH (2 M, 18.93 mL, 24.32 *eq*). The mixture was stirred at 50 °C for 2 hr. LCMS showed starting material was consumed completely and desired product was detected. The reaction mixture was extracted with EtOAc (10 mL x 2).The pH of aqueous phase was adjusted to 5 by HCl (6M in water), and then extracted with EtOAc (10 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 4-chloro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxylic acid (210 mg, 947.22 umol, 60.84% yield, 95% purity) as a light yellow solid.

LCMS (ESI) m/z 210.9 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.51 (br s, 1H), 7.21 (s, 1H), 7.01 (s, 1H), 2.54 (s, 3H).

Synthesis of 4-chloro-N-(1,1-dimethylsilocan-5-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide and 4-chloro-N-(1,1-dimethylsilocan-5-ylidene)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (27.87 mg, 132.33 umol, 1.1 *eq*) and 1,1-dimethylsilocan-5-amine (25 mg, 120.30 umol, 1 *eq*, HCl salt)(containing 7a as impurity) in DMF (1 mL) was added a solution of EDCI (46.12 mg, 240.60 umol, 2 *eq*) and HOBt (32.51 mg, 240.60 umol, 2 *eq*) in DMF (1 mL), followed by TEA (48.69 mg, 481.20 umol, 66.98 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed the reactant was consumed completely and one main peak with desired mass was detected. The

reaction mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 70%-100%B over11min). SFC showed more than 1 peak. The residue from prep-HPLC was further purified by SFC (Sepiatec Prep SFC 100; column: DAICEL CHIRALPAK AD (250mm*30mm,10um particle size); mobile phase: A: 0.1%NH_3H_2O in EtOH, B: CO_2; isocratic 40%B, flow rate: 80 mL/min). Compound 4-chloro-N-(1,1-dimethylsilocan-5-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (18 mg, 49.46 umol, 41.11% yield, 100% purity) was obtained as a white solid.

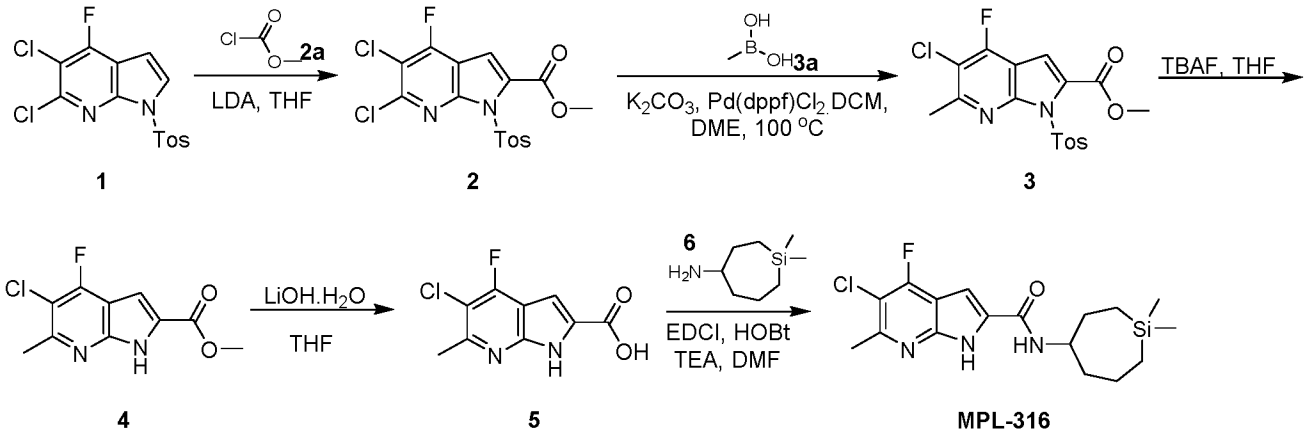
LCMS (ESI) m/z 364.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.18 (s, 1H), 8.35 (d, J=8.1 Hz, 1H), 7.13 (d, J=2.0 Hz, 1H), 7.10 (s, 1H), 3.98 (br d, J=6.1 Hz, 1H), 2.46 (s, 3H), 1.67 - 1.50 (m, 8H), 0.74 - 0.58 (m, 4H), 0.00 (s, 3H), -0.05 (s, 3H).

The same reaction was conducted at 427.32 umol scale. The residue from prep-HPLC purification was further purified by SFC.Compound 4-chloro-N-(1,1-dimethylsilocan-5-ylidene)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (7.4 mg, 20.35 umol, 36.83% yield, 99.5% purity) was obtained as a white solid.

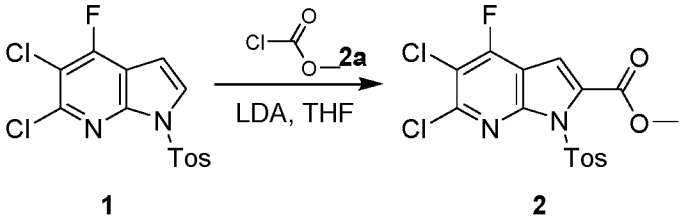
LCMS m/z 362.1 $[M+1]^+$; ^1H NMR (400MHz, METHANOL-d4) δ = 7.16 (s, 1H), 7.07 (s, 1H), 2.76 - 2.64 (m, 2H), 2.60 (s, 3H), 2.53 - 2.46 (m, 1H), 2.28 (br dd, J=2.6, 14.0 Hz, 1H), 1.89 - 1.80 (m, 2H), 1.62 - 1.40 (m, 2H), 0.92 - 0.82 (m, 2H), 0.80 - 0.66 (m, 2H), 0.07 (s, 3H), 0.02 (s, 3H).

Example 151. MPL-316

Scheme

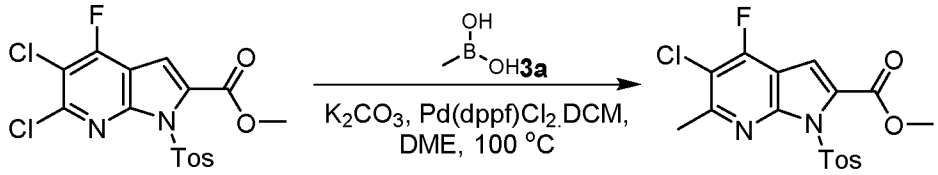


Synthesis of methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



A mixture of 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (3.9 g, 10.86 mmol, 1 eq) in THF (40 mL) was degassed and purged with N_2 for 3 times, then LDA (2 M in THF, 8.14 mL, 1.5 eq) was added and stirred at -60 °C for 10 min under N_2 atmosphere. Methyl carbonochloridate (5.13 g, 54.29 mmol, 4.20 mL, 5 eq) was then added. The mixture was stirred at -60 °C for 30 min. TLC showed one major new spot. The reaction mixture was quenched with saturated NH_4Cl solution (100 mL) at 25 °C, and then diluted with water (50 mL) and extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1). Compound methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.1 g, 2.11 mmol, 19.43% yield, 80% purity) was obtained as a yellow solid. ^1H NMR was recorded.

Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



2 3

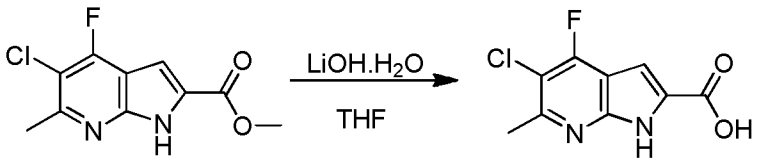
To a mixture of methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.1 g, 2.64 mmol, 1 eq), methylboronic acid (205.16 mg, 3.43 mmol, 1.3 eq) and K_2CO_3 (728.73 mg, 5.27 mmol, 2 eq) was added DME (5 mL). The mixture was purged with N_2 and $Pd(dppf)Cl_2.CH_2Cl_2$ (215.30 mg, 263.64 umol, 0.1 eq) was added under N_2. The mixture was stirred at 100 °C for 12 hr. LC-MS showed desired compound was detected. The reaction mixture was filtered, the cake was washed with EtOAc (20 mL x 3). The combined filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 10/1) to afford methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (553 mg, 1.25 mmol, 47.57% yield, 90% purity) as a yellow solid. ^1H NMR was recorded.

Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate

3 4

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (553 mg, 1.39 mmol, 1 eq) in THF (5 mL) was added TBAF (1 M in THF, 1.81 mL, 1.3 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated the reactant was consumed completely. LCMS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was triturated with water (10 mL) at 25 °C for 30 min, filtered, and the cake was collected. Compound methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (446 mg, crude) was obtained as a yellow solid. ^1H NMR was recorded.

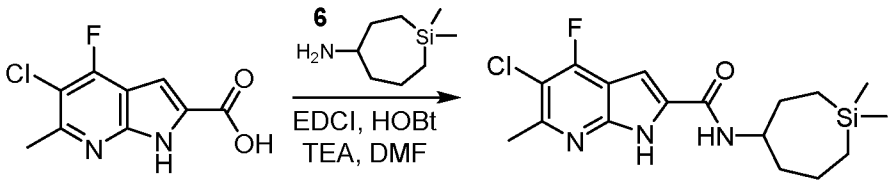
Synthesis of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid



4 5

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (446 mg, 1.84 mmol, 1 eq) in THF (3 mL) was added a solution of $LiOH.H_2O$ (462.78 mg, 11.03 mmol, 6 eq) in H_2O (3 mL). The mixture was stirred at 30 °C for 12 hr. TLC indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure to remove THF. The aqueous phase was adjusted to pH 2 with aqueous HCl (6 M), and then filtered and concentrated under reduced pressure to afford 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (337 mg, 1.33 mmol, 72.18% yield, 90% purity) as a yellow solid. ^1H NMR was recorded. The crude product was used directly for next step without further purification.

Synthesis of 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



5 MPL-316

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 437.43 umol, 1 eq) and 1,1-dimethylsilepan-4-amine (75.70 mg, 390.64 umol, 8.93e-1 eq, HCl salt) in DMF (2 mL) at 25 °C was added a solution of HOBt (177.32 mg, 1.31 mmol, 3 eq) and EDCI (251.57 mg, 1.31 mmol, 3 eq) in DMF (2 mL) with stirring, followed by TEA (221.32 mg, 2.19 mmol, 304.42 uL, 5 eq). The reaction mixture was stirred at 25 °C for 2 hr. LC-MS showed desired compound was detected. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 70%-100%B over 11 min) to afford 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-

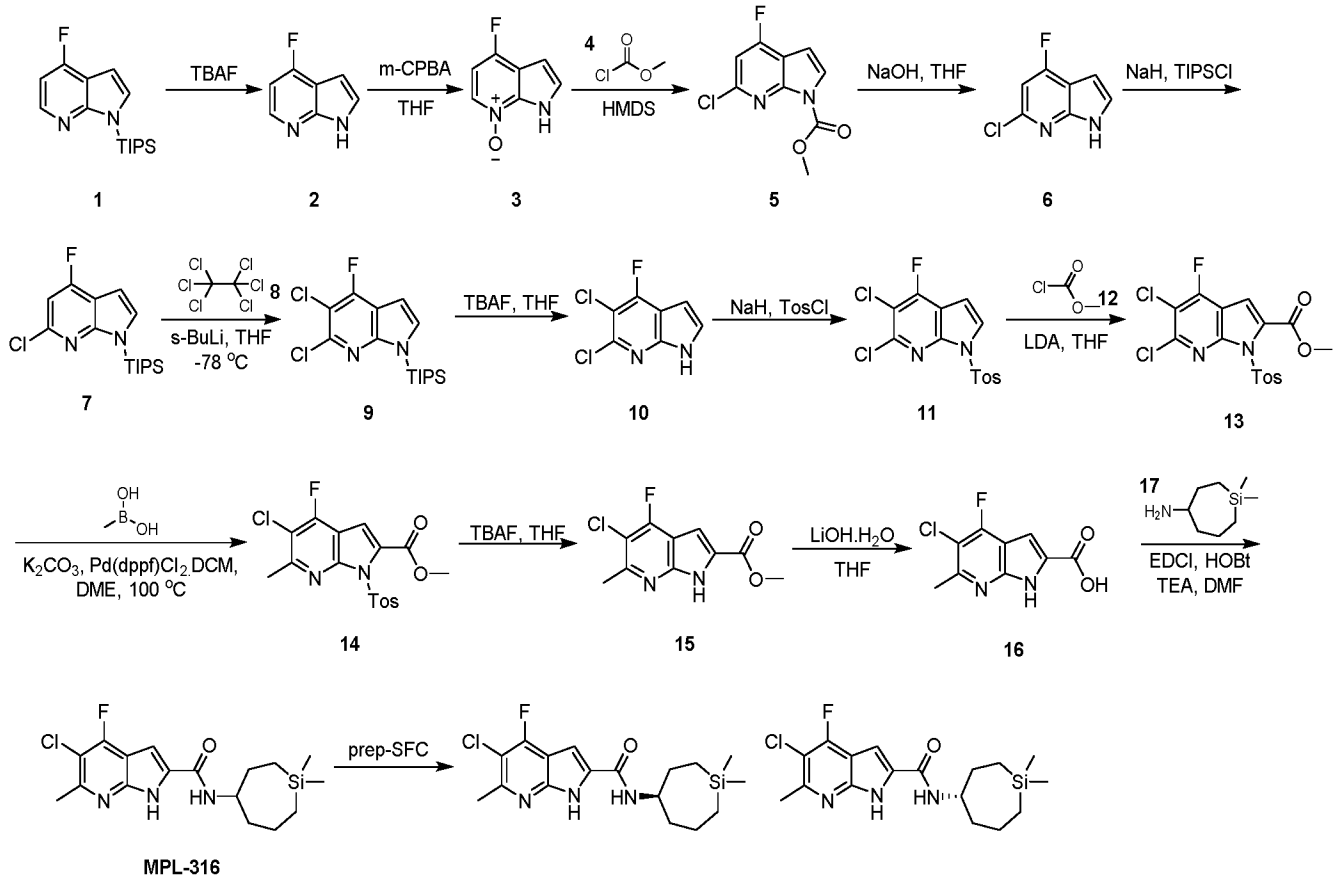
fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (59.4 mg, 152.33 umol, 34.82% yield, 94.352% purity) as a white solid.

LCMS (ESI) m/z 368.1 $[M+H]^+$; ^1H NMR (500MHz, CHLOROFORM-d) δ = 9.37 (br s, 1H), 6.92 - 6.63 (m, 1H), 6.09 (br d, J=7.5 Hz, 1H), 4.06 (br d, J=8.5 Hz, 1H), 2.72 (s, 3H), 2.22 - 1.97 (m, 2H), 1.92 - 1.74 (m, 1H), 1.73 - 1.65 (m, 1H), 1.61 (br s, 1H), 1.51 - 1.41 (m, 1H), 0.87 - 0.59 (m, 4H), 0.06 (d, J=2.0 Hz, 6H).

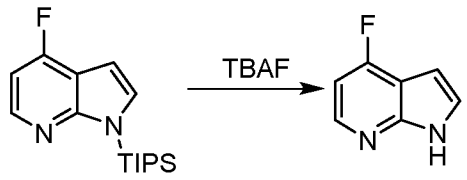
Example 152. MPL-316, MPL-316A and MPL-316B

MPL-316 was also made via different route described in the scheme below and its enantiomers MPL-316A and MPL-316B were obtained after SFC purification.

Scheme:



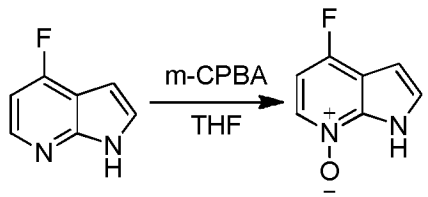
Synthesis of 4-fluoro-1H-pyrrolo[2,3-b]pyridine



1 2

To a solution of (4-fluoropyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (160 g, 547.07 mmol, 1 eq) in THF (300 mL) was added TBAF (1 M in THF, 601.78 mL, 1.1 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated reactant 1 was consumed completely. The reaction mixture was concentrated under reduced pressure and then poured into water, cooled to 0 °C, filtered. The cake was washed with EtOAc (100 mL x 10). The combined aqueous layer was extracted with EtOAc (200 mL x 5). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 0/1). Compound 4-fluoro-1H-pyrrolo[2,3-b]pyridine (82 g, 512.02 mmol, 83.19% yield, 85% purity) was obtained as a pink solid. ^{1}H NMR was recorded.

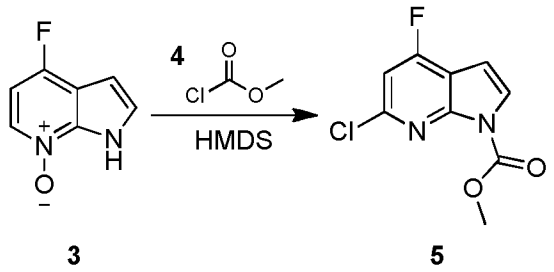
Synthesis of 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium



2 3

To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine (63 g, 462.81 mmol, 1 eq) in THF (500 mL) was added *m*-CPBA (140.94 g, 694.21 mmol, 85% purity, 1.5 eq). The mixture was stirred at 25 °C for 12 hr. TLC indicated the reaction was completed. The reaction mixture was diluted with petroleum ether (500 mL), and then filtered. The cake was collected and dried under reduced pressure. Compound 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (123 g, 404.27 mmol, 87.35% yield, 50% purity) was obtained as a white solid. ^{1}H NMR was recorded. The crude product was used for the next step without further purification.

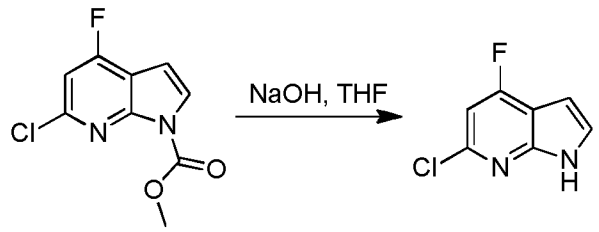
Synthesis of methyl 6-chloro-4-fluoro-pyrrolo[2,3-b]pyridine-1-carboxylate



3 5

To a solution of 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (50 g, 164.34 mmol, 50% purity, 1 eq) in THF (500 mL) was added HMDS (26.52 g, 164.34 mmol, 34.45 mL, 1 eq), followed by methyl carbonochloridate (46.59 g, 493.01 mmol, 38.19 mL, 3 eq) (47.340 g). The mixture was stirred at 50 °C for 1 hr. LC-MS showed desired compound methyl 6-chloro-4-fluoro-pyrrolo[2,3-b]pyridine-1-carboxylate. LCMS (ESI) m/z 229.0 $[M+H]^+$. The reaction mixture was used directly for the next step without any work up.

Synthesis of 6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine

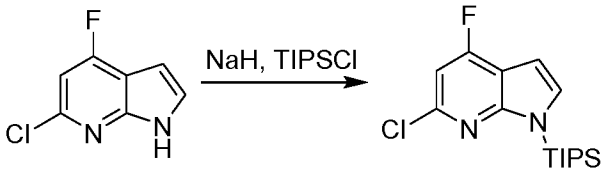


5 6

To the reaction mixture from previous step was added NaOH (3 M, 250 mL, 4.63 eq). The mixture was stirred at 25 °C for 2 hr. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with H_2O (500 mL) and extracted with EtOAc (300 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1) to afford 6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (14 g, 73.87 mmol, 45.64% yield, 90% purity) as a white solid.

LCMS (ESI) m/z 171.0 $[M+H]^+$; ^1H NMR was recorded.

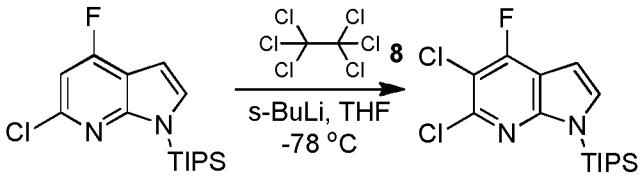
Synthesis of (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



6 7

To a solution of 6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (31 g, 181.74 mmol, 1 eq) in THF (300 mL) was added NaH (21.81 g, 545.23 mmol, 60% purity, 3 eq) at 0 °C under N_2, followed by TIPSCl (42.05 g, 218.09 mmol, 46.67 mL, 1.2 eq) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hr. TLC indicated one major new spot with lower polarity. The reaction mixture was pure into saturated NH_4Cl (300 mL), extracted with EtOAc (200 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 10/1) to afford (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (59 g, 153.41 mmol, 84.41% yield, 85% purity) as a yellow oil. ^1H NMR was recorded.

Synthesis of (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane

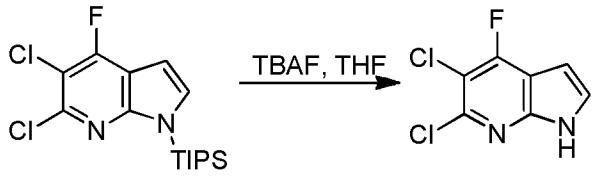


7 9

To a solution of (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (10 g, 30.59 mmol, 1 eq) in THF (100 mL) was added a solution of s-BuLi (1.3 M in n-hexane, 44.71 mL, 1.9 eq). The mixture was stirred at -78 °C for 0.5 hr. Then a solution of 1,1,1,2,2,2-hexachloroethane (10.86 g, 45.88 mmol, 5.20 mL, 1.5 eq) in THF (20 mL) was added. The reaction mixture was stirred at -78 °C for 1.5 hr. LC-MS showed desired compound was detected. The reaction mixture was quenched with saturated NH_4Cl (100 mL) at -78°C, and then extracted with EtOAc mL (200 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2,

petroleum ether/ethyl acetate = 1/0 to 20/1) to afford (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (10 g, 24.91 mmol, 81.42% yield, 90% purity) as a colorless oil. ^{1}H NMR was recorded.

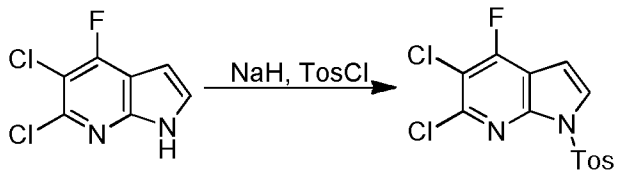
Synthesis of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine



9 **10**

To a solution of (5,6-dichloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (10 g, 17.99 mmol, 65% purity, 1 eq) in THF (100 mL) was added TBAF (1 M in THF, 26.98 mL, 1.5 eq). The mixture was stirred at 25 °C for 30 min. TLC indicated the reaction was completed. The reaction mixture was concentrated under reduced pressure to remove THF. The resulting residue was triturated with water (100 mL) for 20 min, filtered and the cake was washed with petroleum ether (20 mL x 3). The cake was collected and dried under reduced pressure. Compound 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (3.35 g, 14.71 mmol, 81.76% yield, 90% purity) was obtained as a yellow solid, which was used for the next step without further purification. ^{1}H NMR was recorded.

Synthesis of 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



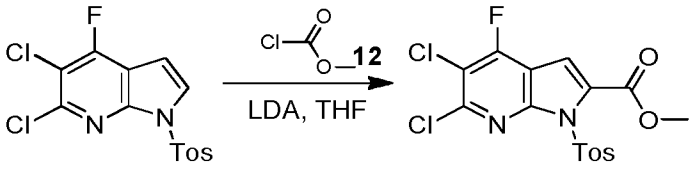
10 **11**

To a mixture of 5,6-dichloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (3.35 g, 16.34 mmol, 1 eq) in THF (50 mL) was added NaH (1.96 g, 49.02 mmol, 60% purity, 3 eq) at 0 °C under N_2, followed by TosCl (4.67 g, 24.51 mmol, 1.5 eq) in THF (30 mL) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hr. LC-MS showed desired compound was detected. The reaction mixture was pure into saturated NH_4Cl (150 mL), and then extracted with EtOAc (100 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2.88 g, 7.22 mmol, 44.16% yield, 90% purity) as a white solid.

LCMS (ESI) m/z 359.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

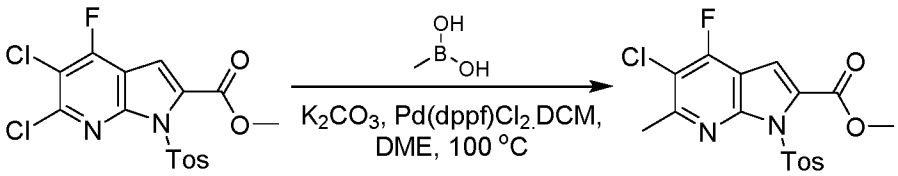


11 13

The reaction was conducted at 8.02 mmol (compound 11 from previous step) using the same procedures described in Example 151 (compound 1 to compound 2). The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford methyl 5,6-dichloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (2.3 g, 4.96 mmol, 61.88% yield, 90% purity) as a white solid.

LCMS (ESI) m/z 419.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

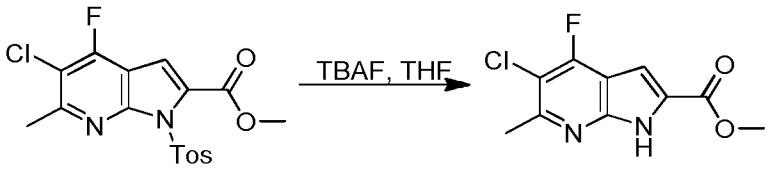


13 14

The reaction was conducted at 5.51 mmol (compound 13 from previous step) using the same procedures described in Example 151 (compound 2 to compound 3). The crude product was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 10/1) to afford methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (436 mg, 988.86 umol, 17.94% yield, 90% purity) as a white solid.

LCMS (ESI) m/z 397.1 $[M+H]^+$; ^1H NMR was recorded.

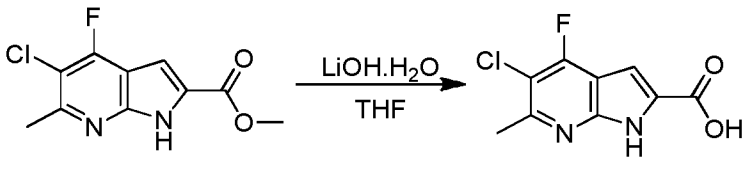
Synthesis of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate



14 **15**

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (436 mg, 1.10 mmol, 1 eq) in THF (5 mL) was added TBAF (1 M HCl, 2 mL, 1.82 eq). The mixture was stirred at 25 °C for 0.5 hr. TLC indicated reactant 14 was consumed completely. The reaction mixture was concentrated under reduced pressure to remove THF. The resulting residue was triturated with water (20 mL) for 20 min, filtered. The cake was collected, washed with petroleum ether (10 mL x 3), and concentrated under reduced pressure. Compound methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (260 mg, 964.42 umol, 87.78% yield, 90% purity) was obtained as a white solid. ^1H NMR was recorded. The crude product was used for the next step without purification.

Synthesis of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

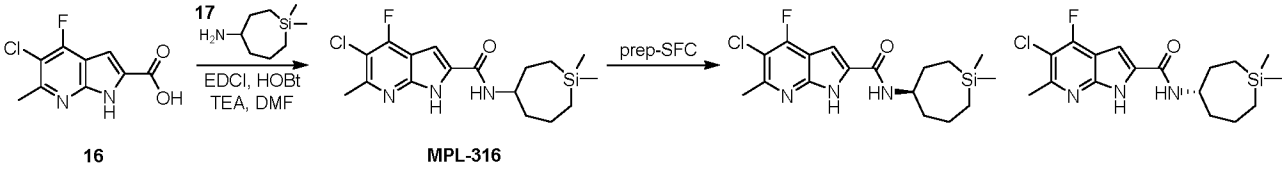


15 **16**

To a solution of methyl 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (260 mg, 1.07 mmol, 1 eq) in THF (5 mL) and H_2O (5 mL) was added $LiOH.H_2O$ (224.82 mg, 5.36 mmol, 5 eq). The mixture was stirred at 25 °C for 12 hr. LC-MS showed desired product was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The residue was diluted with water (10 mL), adjusted to pH to 2 with aqueous HCl (6M), then filtered. The filtrate was concentrated in vacuo to afford crude compound 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (230 mg, 905.48 umol, 84.50% yield, 90% purity) as a white solid.

LCMS (ESI) m/z 229.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide, 5-chloro-N-[(4R)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide and 5-chloro-N-[(4S)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



16 MPL-316

To a solution of 5-chloro-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (150 mg, 656.15 umol, 1 eq) and 1,1-dimethylsilepan-4-amine (152.59 mg, 787.38 umol, 1.2 eq, HCl salt) in DMF (3 mL) at 25 °C was added a solution of HOBt (265.98 mg, 1.97 mmol, 3 eq) and EDCI (377.35 mg, 1.97 mmol, 3 eq) in DMF (2 mL), followed by TEA (331.98 mg, 3.28 mmol, 456.64 uL, 5 eq). The reaction mixture was stirred 25 °C for 2 hr.LC-MS showed desired compound was detected. The mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 65%-95%B over 11min) to afford MPL-316, which was further purified by SFC (Berger MG II, column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: A: 0.1%NH_3H_2O in EtOH, B: CO_2; isocratic 45%B, flow rate: 80 min/mL) to afford two peaks (two enantiomers), 5-chloro-N-[(4R)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide and 5-chloro-N-[(4S)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide.

Peak 1 (MPL-316A): 45.8 mg, 124.48 umol, 18.97% yield, 100% purity, white solid.

LCMS (ESI) m/z 368.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.47 (br s, 1H), 8.34 (d, J=7.9 Hz, 1H), 7.23 (s, 1H), 3.97 - 3.79 (m, 1H), 2.62 (s, 3H), 2.02 - 1.39 (m, 6H), 0.85 - 0.53 (m, 4H), 0.04 (d, J=8.9 Hz, 6H).

Peak 2 (MPL-316B): 51.1 mg, 138.89 umol, 21.17% yield, 100% purity, white solid.

LCMS (ESI) m/z 368.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.47 (br s, 1H), 8.34 (d, *J*=7.9 Hz, 1H), 7.23 (s, 1H), 4.04 - 3.75 (m, 1H), 2.62 (s, 3H), 2.05 - 1.33 (m, 6H), 0.87 - 0.53 (m, 4H), 0.04 (d, *J*=8.9 Hz, 6H).

MPL-316A and MPL-316B were also analyzed by analytical SFC.

Conditions:

Instrument: CAS-SH-ANA-SFC-K (Waters UPCC with PDA Detector)

Column: Chiralpak AD-3 50*4.6mm, 3um particle size

Mobile phase: A: CO_2, B: 0.05% DEA in ethanol

Isocratic: 40% B

Flow rate: 2.5mL/min

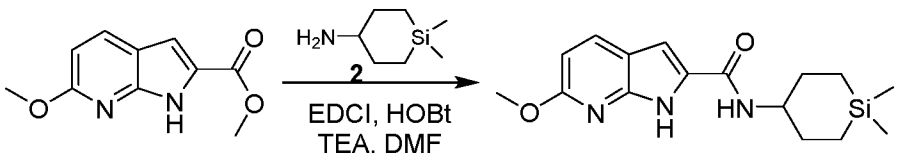
Column temp.: 35 °C

ABPR: 1500 psi

MPL-316A: retention time: 3.47 min; 100% ee; MPL-316B: retention time: 3.85 min; 100% ee.

Example 153. MPL-387

Synthesis of N-(1,1 -dimethylsilinan-4-yl) -6-methoxy- 1H-pyrrolo [2,3-b] pyridine-2-carboxamid



1 **MPL-387**

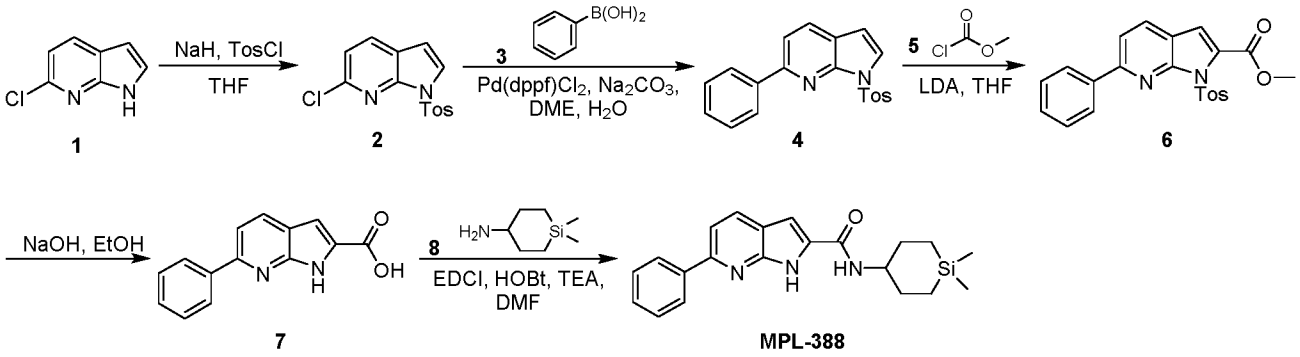
To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 260.18 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (56.13 mg, 312.22 umol, 1.2 eq, HCl salt) in DMF (2 mL) was added a solution of EDCI (149.63 mg, 780.55 umol, 3 eq) and HOBt (105.47 mg, 780.55 umol, 3 eq) in DMF (1 mL), followed by TEA (131.64 mg, 1.30 mmol, 181.07 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired compound was detected. The

reaction mixture was filtered. The filtrated was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 49%-79%B over 11min). Compound N-(1,1 -dimethylsilinan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (62.4 mg, 195.11 umol, 74.99% yield, 99.260% purity) was obtained as a white solid.

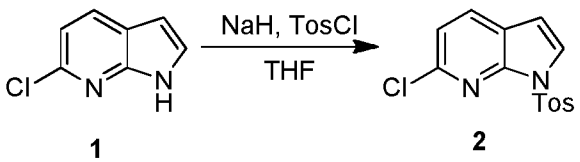
LCMS m/z: 318.1 $[M+1]^+$; ^{1}H NMR (500MHz, DMSO-*d*6) δ = 11.99 - 11.70 (m, 1H), 8.03 - 7.88 (m, 2H), 7.01 (d, *J*=1.8 Hz, 1H), 6.57 (d, *J*=8.5 Hz, 1H), 3.93 - 3.82 (m, 3H), 3.75 - 3.64 (m, 1H), 2.03 - 1.92 (m, 2H), 1.65 - 1.49 (m, 2H), 0.85 - 0.71 (m, 2H), 0.59 (dt, *J*=4.7, 13.9 Hz, 2H), 0.14 - -0.04 (m, 6H).

Example 154. MPL-388

Scheme



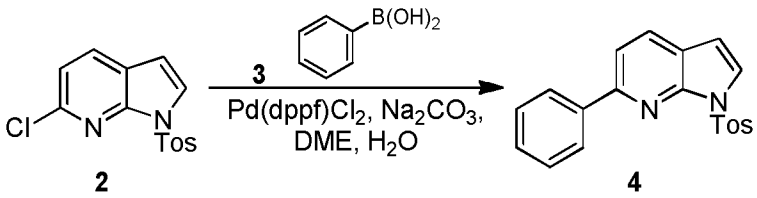
Synthesis of 6-chloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a cooled solution of 6-chloro-1H-pyrrolo[2,3-b]pyridine (2 g, 13.11 mmol, 1 eq) in THF (20 mL) was added NaH (786.39 mg, 19.66 mmol, 60% purity, 1.5 eq) in batches and stirred at 0°C for 30 min. Then to the mixture was added TosCl (3.00 g, 15.73 mmol, 1.2 eq) in batches.The mixture was stirred at 0 °C for 30 min. LC-MS showed desired compound was detected. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 25 °C, and then diluted

with water (10 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 5/1). Compound 6-chloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2.84 g, 8.34 mmol, 63.66% yield, 90% purity) was obtained as a white solid. ^{1}H NMR was recorded.

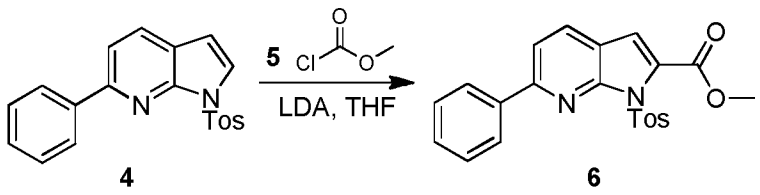
Synthesis of 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a mixture of 6-chloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.3 g, 4.24 mmol, 1 eq), phenylboronic acid (775.06 mg, 6.36 mmol, 1.5 eq) and K_2CO_3 (1.17 g, 8.48 mmol, 2 eq) was added dioxane (15 mL). The mixture was purged with N_2 and $Pd(dppf)Cl_2.CH_2Cl_2$ (346.07 mg, 423.77 umol, 0.1 eq) was added under N_2. The mixture was stirred at 110 °C for 12 hr. LC-MS showed desired compound was detected. The mixture was filtered, the cake was washed with EtOAc (50 mL x 2), the combined filtrate was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate = 1/0 to 3/1) to afford 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.7 g, 4.39 mmol, 90.11% yield, 90% purity) as a brown solid.

LCMS (ESI) m/z 349.1 $[M+H]^+$; ^{1}H NMR was recorded.

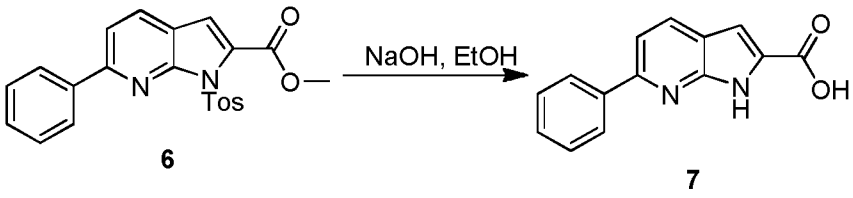
Synthesis of methyl 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



A mixture of 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (498.24 mg, 1.43 mmol, 1 eq) in THF (5 mL) was degassed and purged with N_2 for 3 times, and LDA (2 M in THF, 1.07 mL, 1.5 eq) was then added and stirred at -60 °C for 10 min under N_2 atmosphere. Then methyl carbonochloridate (676.09 mg, 7.15 mmol, 554.17 uL, 5 eq) was added and stirred at -60 °C for 30 min. LC-MS showed desired compound was detected. The reaction mixture was quenched with saturated NH_4Cl (20 mL) at 25 °C, and then diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate = 1/0 to 3/1) to afford methyl 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (463 mg, 1.03 mmol, 71.69% yield, 90% purity) as a brown solid .

LCMS (ESI) m/z 407.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

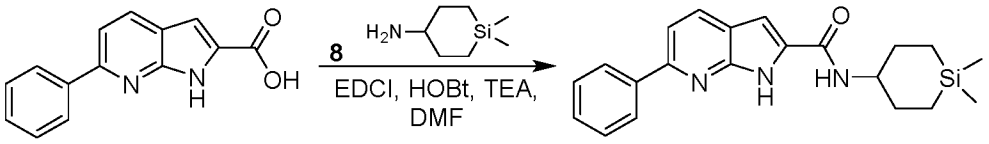


6 **7**

To a solution of methyl 6-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (463 mg, 1.14 mmol, 1 eq) in EtOH (3 mL) was added NaOH (2 M in water, 3 mL, 5.27 eq). The mixture was stirred at 80 °C for 12 hr. TLC showed one major new spot with higher polarity. The reaction mixture was concentrated under reduced pressure to remove EtOH, and then treated with aqueous HCl (6 M) until pH turned to 2, filtered and concentrated under reduced pressure to afford crude 6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (200 mg, 755.54 umol, 66.33% yield, 90% purity) as a yellow solid. It was used for the next step without further purification.

^1H NMR (400MHz, DMSO-d6) δ = 13.12 (br s, 1H), 12.35 (s, 1H), 8.19 - 8.11 (m, 3H), 7.75 (d, J=8.2 Hz, 1H), 7.57 - 7.39 (m, 4H), 7.13 (d, J=2.0 Hz, 1H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



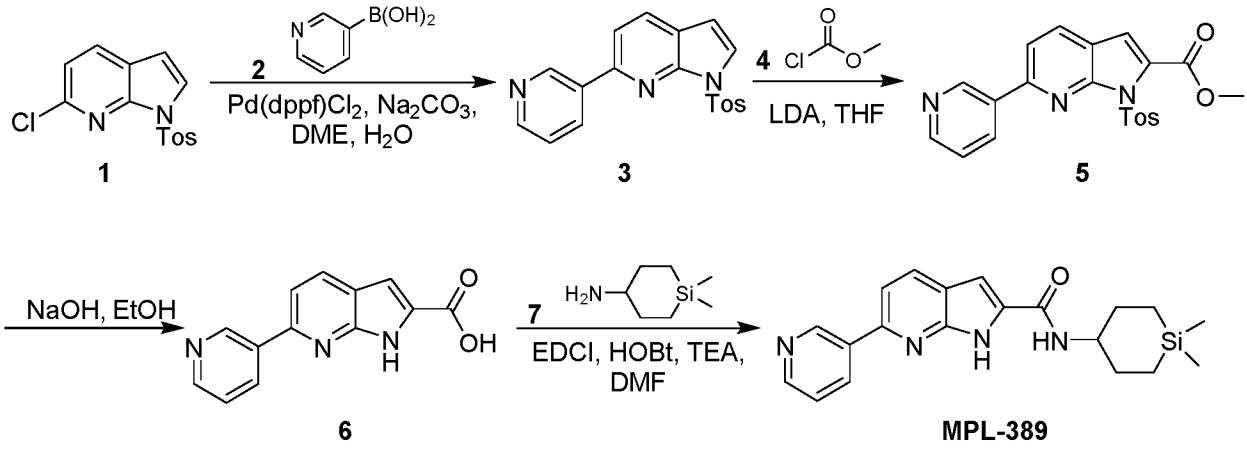
7 MPL-388

To a solution of 6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 209.87 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (41.50 mg, 230.86 umol, 1.1 eq, HCl salt) in DMF (1 mL). was added a solution of HOBt (85.08 mg, 629.61 umol, 3 eq) and EDCI (120.70 mg, 629.61 umol, 3 eq) in DMF (1 mL), followed by TEA (106.18 mg, 1.05 mmol, 146.06 uL, 5 eq). The reaction mixture was stirred at 25 °C for 2 hr. LC-MS showed desired compound was detected. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 64%-94%B over 11min) to afford N-(1,1-dimethylsilinan-4-yl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (42.9 mg, 115.65 umol, 55.11% yield, 98% purity) as a yellow solid.

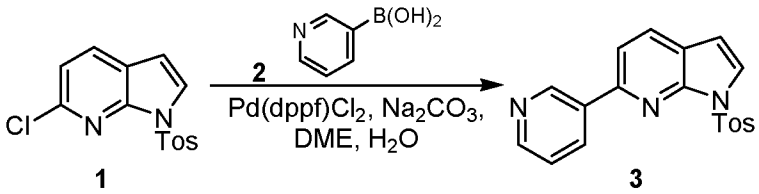
LCMS (ESI) m/z 364.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.07 (s, 1H), 8.21 (d, *J*=8.1 Hz, 1H), 8.16 - 8.07 (m, 3H), 7.71 (d, *J*=8.4 Hz, 1H), 7.53 - 7.46 (m, 2H), 7.44 - 7.37 (m, 1H), 7.12 (d, *J*=2.0 Hz, 1H), 3.78 - 3.66 (m, 1H), 2.05 - 1.92 (m, 2H), 1.67 - 1.51 (m, 2H), 0.87 - 0.54 (m, 4H), 0.15 - 0.01 (m, 6H).

Example 155. MPL-389

Scheme



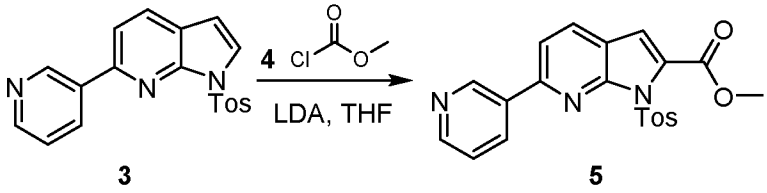
Synthesis of 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine



To a mixture of 6-chloro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.3 g, 4.24 mmol, 1 eq), 3-pyridylboronic acid (781.34 mg, 6.36 mmol, 1.5 eq) and K_2CO_3 (1.17 g, 8.48 mmol, 2 eq) was added dioxane (15 mL) and H_2O (0.1 mL). The mixture was purged with N_2 and $Pd(dppf)Cl_2.CH_2Cl_2$ (346.07 mg, 423.77 umol, 0.1 eq) was added under N_2. The mixture was stirred at 110 °C for 12 hr. LC-MS showed desired compound was detected. The mixture was filtered. The cake was washed with EtOAc (50 mL x 2). The combined filtrate was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 2/1). Compound 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine (967 mg, 2.49 mmol, 58.78% yield, 90% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 350.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine-2-carboxylate

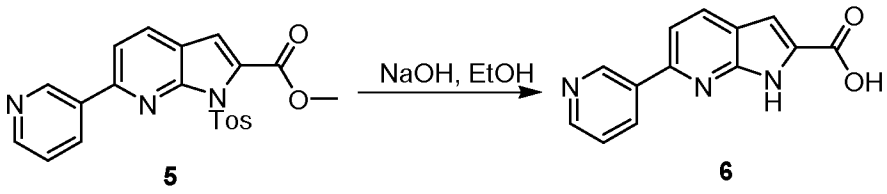


3 5

A mixture of 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine (498.56 mg, 1.43 mmol, 1 eq) in THF (5 mL) was degassed and purged with N_2 for 3 times. LDA (2 M in THF, 1.07 mL, 1.5 eq) was added and stirred at -60 °C for 10 min under N_2 atmosphere. Methyl carbonochloridate (674.18 mg, 7.13 mmol, 552.61 uL, 5 eq) was then added and stirred at -60 °C for 30 min. LC-MS showed desired compound was detected. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) at 25 °C, and then diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, dichloromethane/methanol = 1/0 to 10/1) to afford methyl 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine-2-carboxylate (480 mg, 589.04 umol, 41.28% yield, 50% purity) as a yellow solid.

LCMS (ESI) m/z 408.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

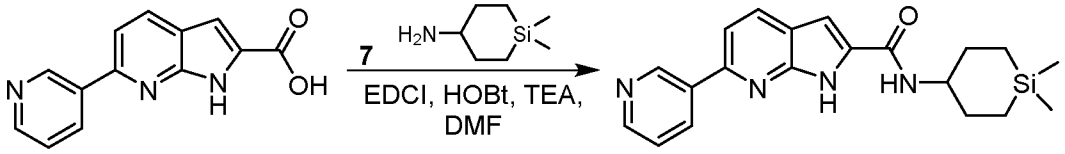


5 6

To a solution of methyl 1-(p-tolylsulfonyl)-6-(3-pyridyl)pyrrolo[2,3-b]pyridine-2-carboxylate (480 mg, 1.18 mmol, 1 eq) in EtOH (3 mL) was added aqueous NaOH (2 M, 3 mL, 5.09 eq). The reaction mixture was stirred at 80 °C for 2 hr. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove EtOH. The aqueous phase was treated with aqueous HCl (6 M) until pH turned to 6, filtered and concentrated under reduced pressure to afford 6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (crude, 240 mg, 802.58 umol, 68.13% yield, 80% purity) as a yellow solid.

LCMS (ESI) m/z 240.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.33 (br s, 1H), 9.31 (d, J=1.6 Hz, 1H), 8.62 (dd, J=1.6, 4.7 Hz, 1H), 8.46 (br d, J=8.2 Hz, 1H), 8.20 (d, J=8.6 Hz, 1H),7.81 (d, J=8.6 Hz, 1H), 7.53 (dd, J=4.7, 7.4 Hz, 1H), 7.14 - 7.03 (m, 1H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



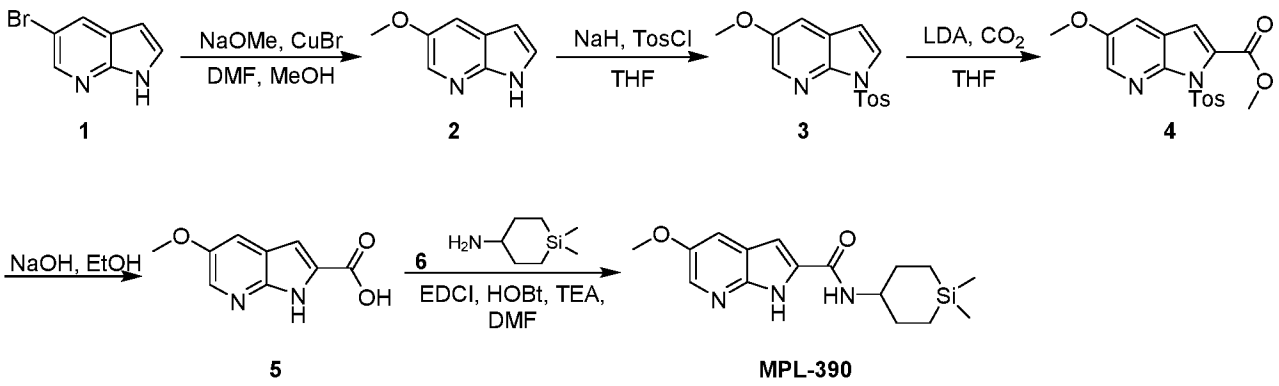
6 MPL-389

To a solution of 6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 209.00 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (41.33 mg, 229.91 umol, 1.1 eq, HCl salt) in DMF (1 mL) was added a solution of HOBt (84.72 mg, 627.01 umol, 3 eq) and EDCI (120.20 mg, 627.01 umol, 3 eq) in DMF (1 mL), followed by TEA (105.74 mg, 1.05 mmol, 145.45 uL, 5 eq). The reaction mixture was stirred at 25 °C for 2 hr. LC-MS showed desired compound was detected. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 45%-75%B over 11min) to afford N-(1,1-dimethylsilinan-4-yl)-6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (31.5 mg, 86.42 umol, 41.35% yield, 100% purity) as a brown solid.

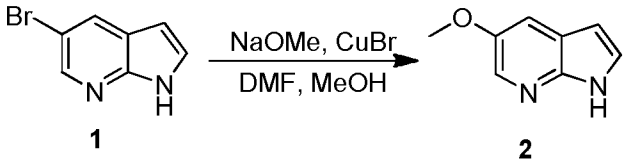
LCMS (ESI) m/z 365.0 $[M+H]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.18 (s, 1H), 9.31 (d, *J*=2.1 Hz, 1H), 8.61 (dd, *J*=1.5, 4.7 Hz, 1H), 8.46 (td, *J*=1.9, 8.0 Hz, 1H), 8.25 (d, *J*=7.9 Hz, 1H), 8.19 (d, *J*=8.2 Hz, 1H), 7.80 (d, *J*=8.4 Hz, 1H), 7.59 - 7.46 (m, 1H), 7.15 (d, *J*=2.0 Hz, 1H), 3.81 - 3.66 (m, 1H), 2.06 - 1.91 (m, 2H), 1.68 - 1.51 (m, 2H), 0.79 (br d, *J*=14.6 Hz, 2H), 0.62 (dt, *J*=4.7, 14.0 Hz, 2H), 0.15 -0.04 (m, 6H).

Example 156. MPL-390

Scheme



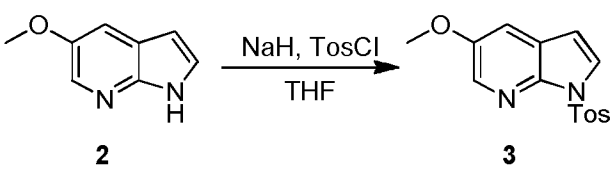
Synthesis of 5-methoxy-1H-pyrrolo[2,3-b]pyridine



To a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (1.24 g, 6.29 mmol, 1 *eq*) in DMF (40 mL) and MeOH (30 mL) was added CuBr (1.81 g, 12.59 mmol, 383.35 uL, 2 *eq*) and sodium methanolate (18.02 g, 333.55 mmol, 53 *eq*). The mixture was stirred at 130 °C for 4 hr under N_2 atmosphere. LC-MS showed desired product was detected. The reaction mixture was filtered and concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (200 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (30 mL x **2**), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, dichloromethane/ methanol = 1/0 to 10/1). Compound 5-methoxy-1H-pyrrolo[2,3-b]pyridine (641 mg, 3.68 mmol, 50.37% yield, 85% purity) was obtained as a brown solid.

LCMS m/z: 149.1 $[M+1]^+$; ^1H NMR was recorded.

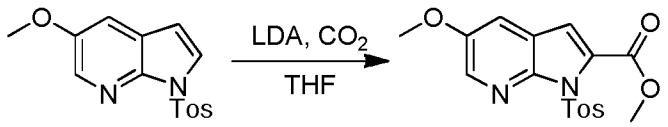
Synthesis of 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 5-methoxy-1H-pyrrolo[2,3-b]pyridine (641 mg, 4.33 mmol, 1 *eq*) in THF (8 mL) was added NaH (259.56 mg, 6.49 mmol, 60% purity, 1.5 *eq*). The mixture was stirred at 0 °C for 30 mins. TosCl (907.29 mg, 4.76 mmol, 1.1 *eq*) was then added. The mixture was stirred at 0 °C for 30 mins. LC-MS showed desired mass was detected. The reaction was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=1/0 to 5/1) to afford 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.10 g, 3.45 mmol, 79.82% yield, 95% purity) as a white solid.

LCMS m/z: 303.1 $[M+1]^+$; ^1H NMR was recorded.

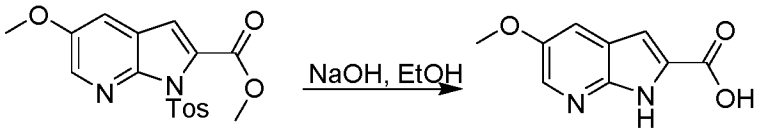
Synthesis of methyl 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



3 **4**

To a solution of 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.10 g, 3.64 mmol, 1 *eq*) in THF (10 mL) was added LDA in THF (2 M, 2.73 mL, 1.5 *eq*) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 min. Methyl carbonochloridate (1.72 g, 18.19 mmol, 1.41 mL, 5 *eq*) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 mins. TLC (Petroleum ether : Ethyl acetate=3:1) indicated new spots formed. The reaction mixture was quenched with saturated NH_4Cl (20 mL), extracted with EtOAc (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1) to afford methyl 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (514 mg, 1.35 mmol, 37.24% yield, 95% purity) as a white solid. ^1H NMR was recorded.

Synthesis of 5-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

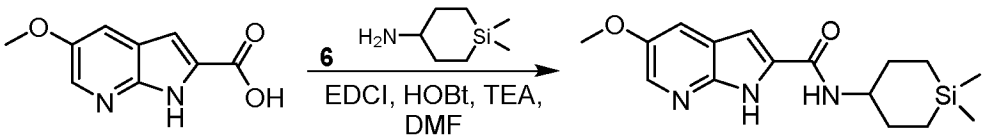


4 5

To a solution of methyl 5-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (514 mg, 1.43 mmol, 1 *eq*) in EtOH (6 mL) was added aqueous NaOH (2 M, 6 mL, 8.41 *eq*). The mixture was stirred at 80 °C for 2 hr. LC-MS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove EtOH. The aqueous solution was adjusted to pH to 3-4 with aqueous HCl (6 N) and filtered. The cake was washed with petroleum ether (15 mL) and dried under reduced pressure. Compound 5-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (245 mg, 1.21 mmol, 84.92% yield, 95% purity) was obtained as a white solid

LCMS m/z: 193.1 $[M+1]^+$; ^1H NMR (400 MHz, DMSO-*d*6) δ = 13.40 - 12.69 (m, 1H), 12.29 - 12.08 (m, 1H), 8.14 (d, J=2.9 Hz, 1H), 7.61 (d, J=2.7 Hz, 1H), 7.01 (d, J=2.1 Hz, 1H), 3.82 (s, 3H).

Synthesis of N-(1, 1-dimethylsilinan-4-yl)-5-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide



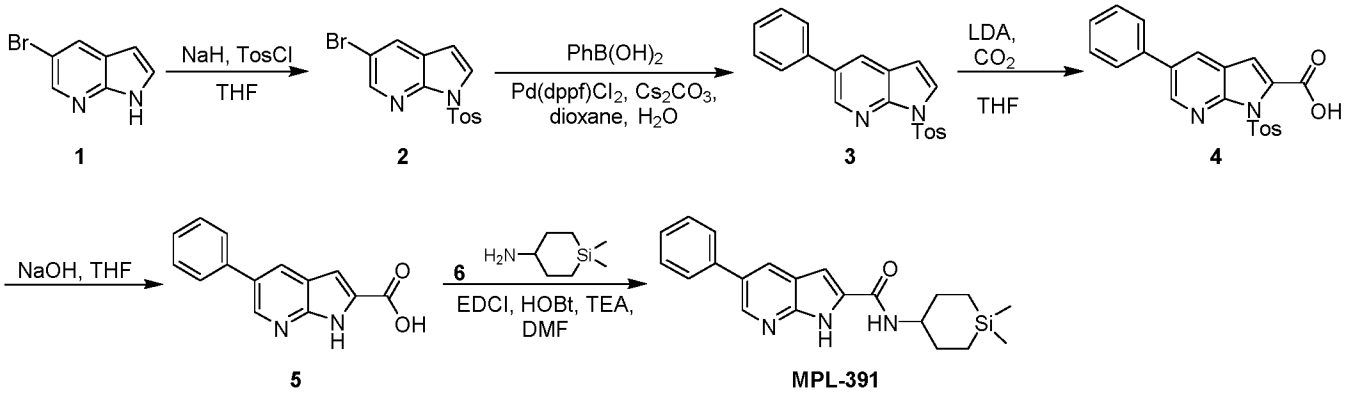
5 MPL-390

To a solution of 5-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 260.18 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (56.13 mg, 312.22 umol, 1.2 *eq*, HCl salt) in DMF (2 mL) was added a solution of EDCI (149.63 mg, 780.55 umol, 3 *eq*) and HOBt (105.47 mg, 780.55 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (157.97 mg, 1.56 mmol, 217.29 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered to obtain filtrate. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient:52%-82%B over 11min) to afford N-(1, 1-dimethylsilinan-4-yl)-5-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide (57.4 mg, 180.74 umol, 69.47% yield, 99.960% purity) as a white solid.

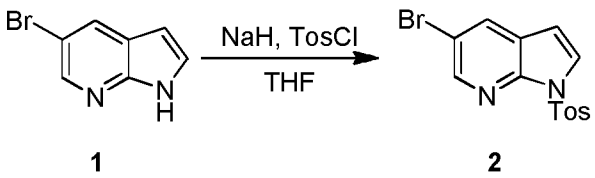
LCMS m/z: 318.0 $[M+1]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 11.88 (br s, 1H), 8.17 (d, *J*=8.1 Hz, 1H), 8.06 (d, *J*=2.9 Hz, 1H), 7.59 (d, *J*=2.7 Hz, 1H), 7.08 - 6.91 (m, 1H), 3.84 - 3.78 (m, 3H), 3.75 - 3.66 (m, 1H), 2.05 - 1.93 (m, 2H), 1.66 - 1.52 (m, 2H), 0.78 (br d, *J*=14.5 Hz, 2H), 0.61 (dt, *J*=4.8, 14.1 Hz, 2H), 0.11 -0.01 (m, 6H).

Example 157. MPL-391

Scheme



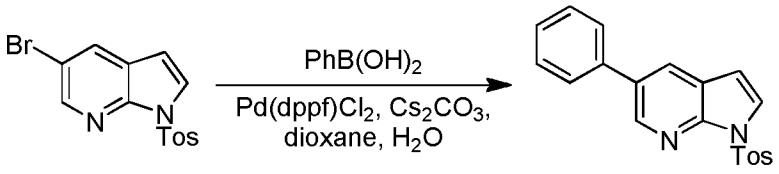
Synthesis of 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (2 g, 10.15 mmol, 1 *eq*) in THF (20 mL) was added NaH (608.98 mg, 15.23 mmol, 60% purity, 1.5 *eq*). The mixture was stirred at 0 °C for 30 mins. Then TosCl (2.13 g, 11.17 mmol, 1.1 *eq*) was added. The mixture was stirred at 0 °C for 30 mins. TLC (Petroleum ether : Ethyl acetate=10:1) indicated many new spots formed. The reaction was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 10/1) to afford 5-bromo-1-(p-

tolylsulfonyl)pyrrolo[2,3-b]pyridine (3.01 g, 7.72 mmol, 76.01% yield, 90% purity) as a white solid. ^{1}H NMR was recorded.

Synthesis of 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

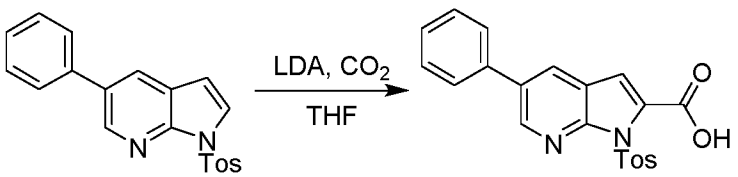


2 **3**

To a mixture of 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.5 g, 4.27 mmol, 1 *eq*), phenylboronic acid (624.89 mg, 5.13 mmol, 1.2 *eq*) and Cs_2CO_3 (2.78 g, 8.54 mmol, 2 *eq*) in dioxane (0.5 mL) and H_2O (5 mL) was added $Pd(dppf)Cl_2$ (312.50 mg, 427.09 umol, 0.1 *eq*) under N_2. The mixture was heated at 110 °C for 12 hrs. LC-MS indicated desired product was detected. The mixture was diluted with EtOAc (30 mL) and filtered to remove insoluble materials. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 25/3). Compound 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.36 g, 3.32 mmol, 77.69% yield, 85% purity) was obtained as a colorless oil.

LCMS m/z: 349.1 $[M+1]^+$; ^{1}H NMR was recorded.

Synthesis of methyl 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

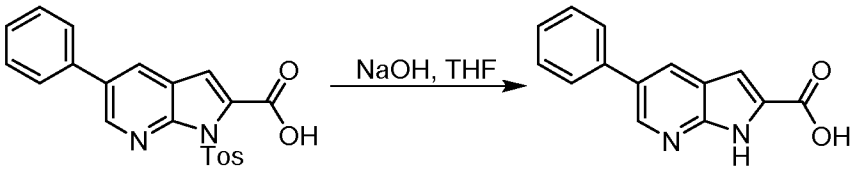


3 **4**

To a solution of 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.36 g, 3.90 mmol, 1 *eq*) in THF (12 mL) was added LDA (2 M in THF, 2.93 mL, 1.5 *eq*) dropwise at -78 °C under N_2. After strring at -78 °C for 30 min, methyl carbonochloridate (1.84 g, 19.52 mmol, 1.51 mL, 5 *eq*) was added dropwise at -78 °C, and the reaction mixture was stirred at -78 °C for another 30 min. TLC (Petroleum ether : Ethyl acetate=5:1) indicated new spots were formed. The reaction

mixture was quenched with NH_4Cl (20 mL) and extracted with EtOAc (30 mL x 2). The combined organic layer waswashed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 5/1). Compound methyl 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (317 mg, 701.93 umol, 17.98% yield, 90% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of 5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

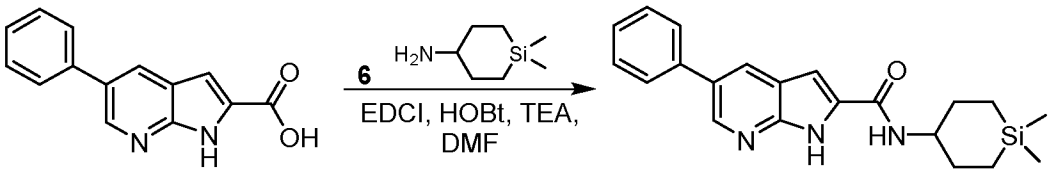


4 **5**

To a solution of methyl 5-phenyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (317 mg, 779.92 umol, 1 *eq*) in EtOH (5 mL) was added aqueous NaOH (2 M, 5 mL, 12.82 *eq*). The mixture was stirred at 80 °C for 2 hr. Desired product was detected by LC-MS. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residual solution was adjusted to pH 3-4 with aqueous HCl (6 N), and then filtered. The cake was washed with petroleum ether (15 mL) and dried under reduced pressure. Compound 5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (163 mg, 615.76 umol, 78.95% yield, 90% purity) was obtained as a yellow solid. It was used for the next step without further purification.

LCMS m/z: 239.1 $[M+1]^+$; ^1H NMR (500MHz, DMSO-*d*6) δ = 12.43 (s, 1H), 8.73 (, 1H), 8.35 - 8.39 (s, 1H), 7.53-7.76 (d, J=7.5 Hz, 2H), 7.48-7.53 (t, J=7.5 Hz, 2H), 7.37 - 7.40 (m, 1H), 7.16 (s, 1H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine- 2-carboxamide



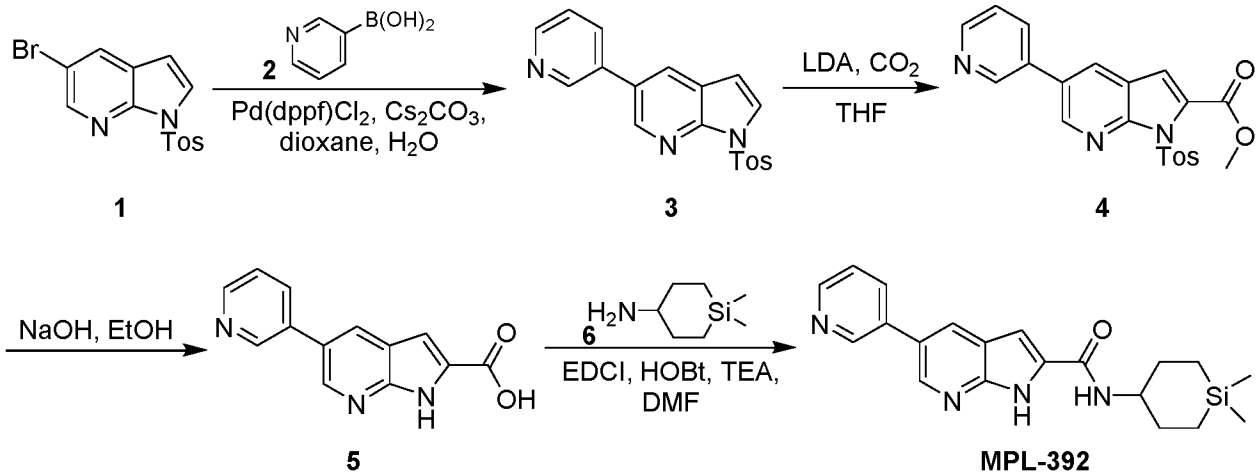
5 **MPL-391**

To a solution of 5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 209.87 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (45.27 mg, 251.85 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (120.70 mg, 629.61 umol, 3 *eq*) and HOBt (85.08 mg, 629.61 umol, 3 *eq*) in DMF (1 mL), followed by TEA (127.42 mg, 1.26 mmol, 175.27 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LC-MS indicated desired product was formed. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 66%-95% over 11min) to afford N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (48.8 mg, 133.42 umol, 63.57% yield, 99.39% purity) as a white solid.

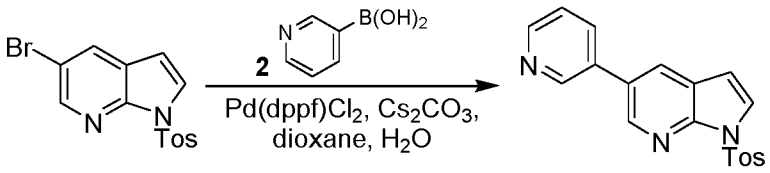
LCMS m/z: 239.1 $[M+1]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 12.12 (s, 1H), 8.62 (d, *J*=2.1 Hz, 1H), 8.36 - 8.21 (m, 2H), 7.73 (d, *J*=7.3 Hz, 2H), 7.49 (t, *J*=7.7 Hz, 2H), 7.42 - 7.30 (m, 1H), 7.22 - 7.09 (m, 1H), 3.78 - 3.67 (m, 1H), 2.06 - 1.95 (m, 2H), 1.68 - 1.54 (m, 2H), 0.79 (br d, *J*=14.6 Hz, 2H), 0.62 (dt, *J*=4.7, 14.0 Hz, 2H), 0.14 - 0.02 (m, 6H).

Example 158. MPL-392

Scheme



Synthesis of 1-(p-tolylsulfonyl)-5-(3-pyridyl)pyrrolo[2,3-b]pyridine

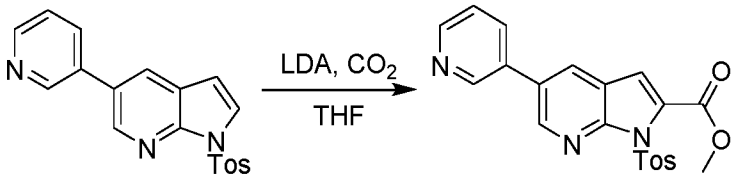


1 3

To a solution of 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2.18 g, 6.21 mmol, 1 *eq*), 3-pyridylboronic acid (915.53 mg, 7.45 mmol, 1.2 *eq*) and Cs_2CO_3 (4.04 g, 12.41 mmol, 2 *eq*) in dioxane (20 mL) and H2O (2 mL) was added Pd(dppf)Cl_2 (454.17 mg, 620.70 umol, 0.1 *eq*) under N_2. The mixture was heated at 110 °C for 12 hrs. LC-MS showed desired product was detected. The mixture was diluted with EtOAc (30 mL) and filtered to remove the insoluble solid. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 5/3). Compound 1-(p-tolylsulfonyl)-5-(3-pyridyl)pyrrolo[2,3-b]pyridine (1.86 g, 4.80 mmol, 77.35% yield, 90% purity) was obtained as a yellow solid.

LCMS m/z: 350.1 $[M+1]^+$; ^1H NMR was recorded.

Synthesis of methyl 1-(p-tolylsulfonyl)-5-(3-pyridyl) pyrrolo[2,3-b] pyridine-2-carboxylate

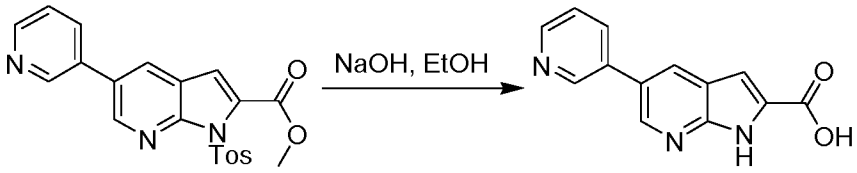


3 4

To a solution of 1-(p-tolylsulfonyl)-5-(3-pyridyl)pyrrolo[2,3-b]pyridine (1.86 g, 5.33 mmol, 1 *eq*) in THF (20 mL) was added LDA (2 M in THF, 4.00 mL, 1.5 *eq*) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 min. Methyl carbonochloridate (2.52 g, 26.67 mmol, 2.07 mL, 5 *eq*) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 min. TLC (Petroleum ether : Ethyl acetate=1:1) indicated compound 3 was remained and new spots formed. The reaction mixture was quenched with saturated NH_4Cl (50

mL) and extracted with dichloromethane (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1). Compound methyl 1-(p-tolylsulfonyl)-5-(3-pyridyl) pyrrolo[2,3-b] pyridine-2-carboxylate (1.36 g, 2.34 mmol, 43.80% yield, 70% purity) was obtained as a white solid. ^1H NMR was recorded. It was used for the next step without further purification.

Synthesis of 5-(3-pyridyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid

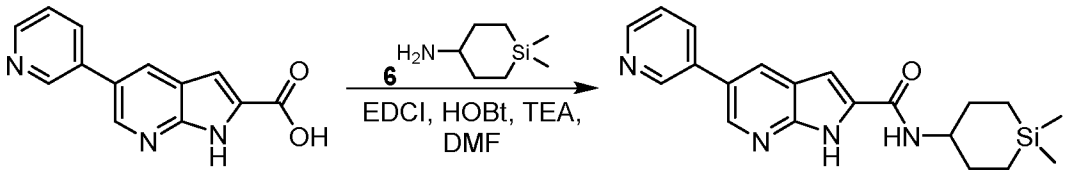


4 **5**

To a solution of methyl 1-(p-tolylsulfonyl)-5-(3-pyridyl)pyrrolo[2,3-b]pyridine-2-carboxylate (700 mg, 1.72 mmol, 1 *eq*) in EtOH (10 mL) was added aqueous NaOH (2 M, 859.02 uL, 1 *eq*). The mixture was stirred at 80 °C for 2 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (8 mL) and extracted with dichloromethane (10 mL x 3). The aqueous phase was adjusted to pH 6-7 with aqueous HCl (6 N) and filtered. The filter cake was washed with petroleum ether (10 mL) and dried under reduced pressure. Compound 5-(3-pyridyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid (270 mg, 1.07 mmol, 62.41% yield, 95% purity) was obtained as a white solid. It was used for the next step without further purification.

LCMS m/z: 240.1 $[M+1]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 13.25 (br, s, 1H), 12.51 (s, 1H), 8.97 (s, 1H), 8.75 (s, 1H), 8.59 (s, 1H), 8.44 (s, 1H), 8.16-8.18 (d, *J*=7.5 Hz, 1H), 7.51-7.54 (m, 1H), 7.17 (s, 1H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

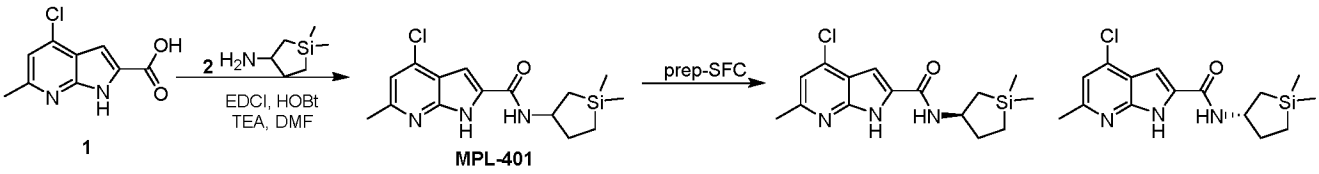


5 MPL-392

To a solution of 5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 209.00 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (45.09 mg, 250.81 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (40.07 mg, 209.00 umol, 1 *eq*) and HOBt (28.24 mg, 209.00 umol, 1 *eq*) in DMF (1 mL), followed by TEA (21.15 mg, 209.00 umol, 29.09 uL, 1 *eq*). The mixture was stirred at 25 °C for 1 hr. LC-MS indicated desired product was detected. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 42%-72% B over 11min). Compound N-(1,1-dimethylsilinan-4-yl)-5-(3-pyridyl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (41 mg, 111.67 umol, 53.43% yield, 99.279% purity) was obtained as a white solid.

LCMS m/z: 365.1 $[M+1]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.21 (s, 1H), 8.97 (d, *J*=2.0 Hz, 1H), 8.99 - 8.93 (m, 1H), 8.68 (d, *J*=2.1 Hz, 1H), 8.58 (d, *J*=3.8 Hz, 1H), 8.42 (d, *J*=2.1 Hz, 1H), 8.32 (d, *J*=8.1 Hz, 1H), 8.16 (br d, *J*=7.9 Hz, 1H), 7.51 (dd, *J*=4.7, 7.9 Hz, 1H), 7.23 - 7.16 (m, 1H), 3.79 - 3.67 (m, 1H), 2.08 - 1.95 (m, 2H), 1.68 - 1.54 (m, 2H), 0.79 (br d, *J*=14.5 Hz, 2H), 0.62 (dt, *J*=4.7, 14.0 Hz, 2H), 0.10 (s, 3H), 0.04 (s, 3H).

Example 159: MPL-401, MPL-401A and MPL-401B



1 MPL-401

Synthesis of 4-chloro-N-(1,1-dimethylsilolan-3-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide, 4-chloro-N-[(3R)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide,and 4-chloro-N-[(3S)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo [2,3-b] pyridine-2 -carboxamide

To a solution of 4-chloro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 142.44 umol, 1 *eq*) and 1,1-dimethylsilolan-3-amine (25.97 mg, 156.68 umol, 1.1 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (54.61 mg, 284.88 umol, 2 *eq*) and HOBt (38.49 mg, 284.88 umol, 2 *eq*) in DMF (1 mL), followed by TEA (57.65 mg, 569.76 umol, 79.30 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed reactant 1 was consumed completely and one main peak with desired mass. The mixture was diluted with MeOH (2 mL) and filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 57%-87%B over 11min). Compound 4-chloro-N-(1,1-dimethylsilolan-3-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (27.9 mg, 86.68 umol, 60.85% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 322.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.08 (s, 1H), 8.21 (br d, *J*=7.6 Hz, 1H), 7.01 (d, *J*=2.2 Hz, 1H), 6.98 (s, 1H), 3.92 - 3.77 (m, 1H), 2.35 (s, 3H), 1.92 - 1.81 (m, 1H), 1.27 (dq, *J*=7.2, 12.1 Hz, 1H), 0.98 - 0.89 (m, 1H), 0.64 (br dd, *J*=5.5, 14.6 Hz, 1H), 0.48 (dd, *J*=11.2, 14.2 Hz, 1H), 0.41 - 0.30 (m, 1H), 0.00 (d, *J*=1.5 Hz, 6H).

The same reaction was conducted later at 427.3 umol. The product (MPL-401) from prep-HPLC purification was separated by prep-SFC (Waters Prep SFC 80Q; Column: (s,s) WHELK-O1 (250mm*30mm, 5um); mobile phase: A: 0.1%NH_3H_2O in IPA, B: CO_2, isocratic 30%B, flow rate: 40 mL/min) to yield two peaks (two enantiomers), 4-chloro-N-[(3R)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide,and4-chloro-N-[(3S)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo [2,3-b] pyridine-2 -carboxamide.

Peak 1 (MPL-401A) (12.8 mg, 38.47 umol, 35.3% yield, 96.7% purity) was obtained as a white solid.

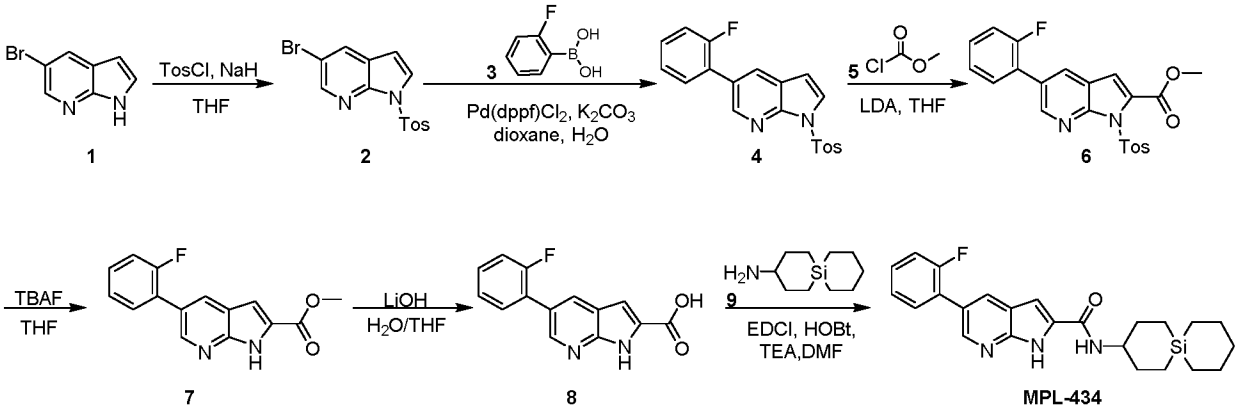
LCMS m/z: 322.0 $[M+1]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.24 (br s, 1H), 8.38 (d, *J*=7.4 Hz, 1H), 7.17 (d, *J*=11.7 Hz, 2H), 4.09 - 3.95 (m, 1H), 2.52 (s, 3H), 2.03 (br d, *J*=4.3 Hz, 1H), 1.44 (dq, *J*=7.0, 12.0 Hz, 1H), 1.11 (br dd, *J*=5.1, 14.1 Hz, 1H), 0.81 (br dd, *J*=5.3, 14.7 Hz, 1H), 0.65 (dd, *J*=11.2, 14.3 Hz, 1H), 0.58 - 0.47 (m, 1H), 0.18 (d, *J*=1.6 Hz, 6H).

Peak 2 (MPL-401B) (42.4 mg, 131.73 umol, 30.3% yield, 100% purity) was obtained as a white solid.

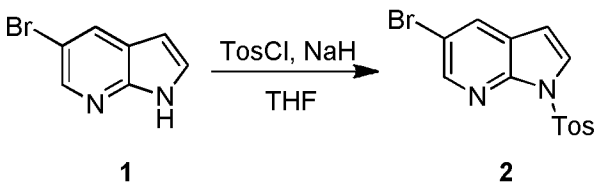
LCMS m/z: 322.0 $[M+1]^+$; [1] 1H NMR (500MHz, DMSO-d6) δ = 12.24 (br s, 1H), 8.38 (d, *J*=7.6 Hz, 1H), 7.17 (d, *J*=15.0 Hz, 2H), 4.02 (dq, *J*=7.0, 11.6 Hz, 1H), 2.52 (s, 3H), 2.09 - 1.98 (m, 1H), 1.44 (dq, *J*=7.2, 12.1 Hz, 1H), 1.16 - 1.06 (m, 1H), 0.86 - 0.77 (m, 1H), 0.65 (dd, *J*=11.1, 14.1 Hz, 1H), 0.53 (ddd, *J*=7.9, 12.6, 14.6 Hz, 1H), 0.17 (d, *J*=2.1 Hz, 6H).

Example 160. MPL-434

Scheme



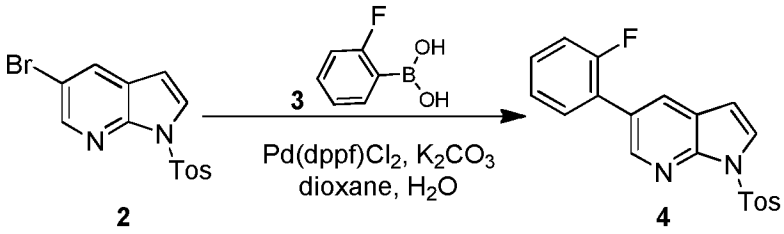
Synthesis of 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 5-bromo-1H-pyrrolo[2,3-b]pyridine (10 g, 50.75 mmol, 1 eq) in THF (100 mL) was added NaH (6.09 g, 152.26 mmol, 60% purity, 3 eq), followed by TosCl (14.51 g, 76.13 mmol, 1.5 eq) at 0 °C. The mixture was stirred at 0 °C for 2 hr. TLC indicated that desired product was detected. The reaction mixture was quenched with aqueous NH_4Cl (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column

chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 10/1) to afford 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (12 g, 30.75 mmol, 60.59% yield, 90% purity) as a yellow solid. ^1H NMR was recorded.

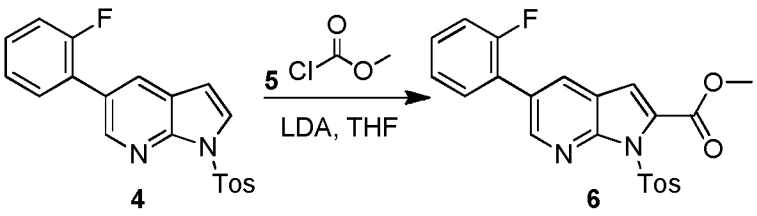
Synthesis of 5-(2-fluorophenyl)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a mixture of 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (200 mg, 569.45 umol, 1 eq), (2-fluorophenyl)boronic acid (239.03 mg, 1.71 mmol, 3 eq) and K_2CO_3 (236.10 mg, 1.71 mmol, 3 eq) in dioxane (5 mL) was added H_2O (0.05 mL). The mixture was purged with N_2, $Pd(dppf)Cl_2$ (41.67 mg, 56.94 umol, 0.1 eq) was then added under N_2. The mixture was stirred at 120 °C for 12 hr under N_2. LCMS showed desired mass. The mixture was filtered. The cake was washed with EtOAc (10 mL x 3). The combined filtrate was dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 1/1). Compound 5-(2-fluorophenyl)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (200 mg, 436.67 umol, 76.68% yield, 80% purity) was obtained as a yellow solid.

LCMS (ESI) m/z: 367.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 5-(2-fluorophenyl)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate

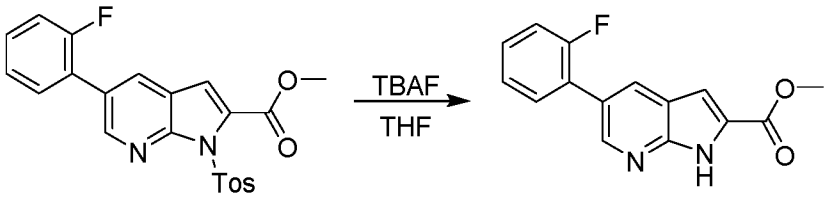


A mixture of 5-(2-fluorophenyl)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2.2 g, 6.00 mmol, 1 eq) in THF (25 mL) was degassed and purged with N_2 for 3 times. LDA (2 M in THF, 4.50 mL, 1.5 eq) was added and the reaction mixture was stirred at -60 °C for 10 min under N_2

atmosphere. Methyl carbonochloridate (2.84 g, 30.02 mmol, 2.33 mL, 5 eq) was then added and the mixture was stirred at -60 °C for 30 min. LC-MS showed that desired compound was detected. The reaction mixture was quenched with saturated NH_4Cl solution 50 mL at 25 °C, and then diluted with water (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, dichloromethane/methanol = 1/0 to 5/1). Compound methyl 5-(2-fluorophenyl)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (900 mg, 1.70 mmol, 28.25% yield, 80% purity) was obtained as a yellow oil.

LCMS (ESI) m/z: 408.1 $[M+H]^+$; ^1H NMR was recorded.

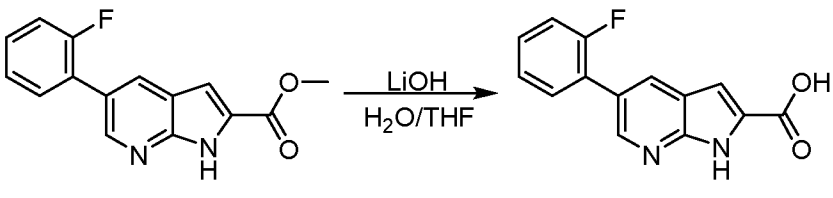
Synthesis of methyl 5-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate



6 **7**

To a solution of methyl 1-(p-tolylsulfonyl)-5-(3-pyridyl)pyrrolo[2,3-b]pyridine-2-carboxylate (800 mg, 1.96 mmol, 1 eq) in THF (10 mL) was added TBAF in THF (1 M, 2.95 mL, 1.5 eq). The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (10 mL) and filtered to obtain compound methyl 5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (500 mg, crude) as a yellow solid. It was used for the next step without purification.

Synthesis of 5-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

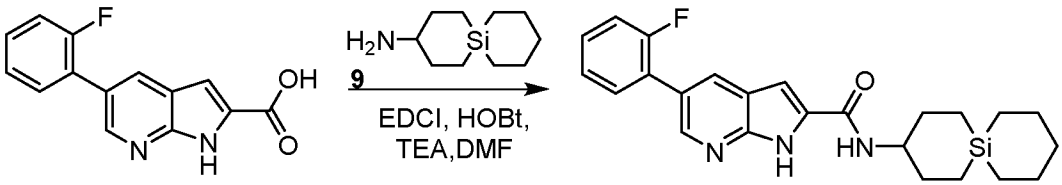


7 **8**

To a solution of methyl 5-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (400 mg, crude, 1.48 mmol, 1 eq) in EtOH (10 mL) was added a solution of $LiOH.H_2O$ (1.24 g, 29.60 mmol, 20 eq) in H_2O (5 mL), the mixture was stirred at 80 °C for 1 hr. TLC showed that reactant was consumed, and new spot was formed. The mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with water (10 mL), acidified to pH 7 with 1 N HCl, extracted with EtOAc (20 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford compound 5-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (300 mg, 936.65 umol, 63.28% yield, 80% purity) as a yellow solid. The crude product was used for the next step without further purification.

^1H NMR (500MHz, DMSO-d6) δ = 12.50 (s, 1H), 8.55 (s, 1H), 8.27 (s, 1H), 7.62 (br t, J=7.9 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.39 - 7.32 (m, 2H), 7.18 (d, J=1.8 Hz, 1H).

Synthesis of 5-(2-fluorophenyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



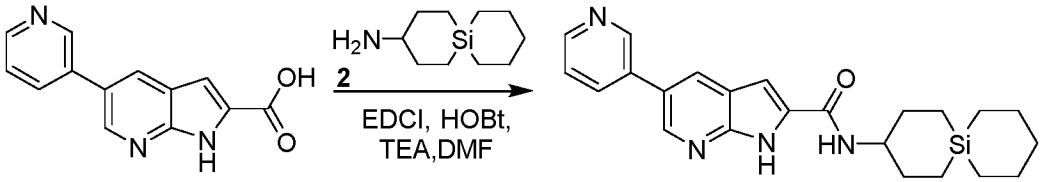
8 **MPL-434**

To a solution of 5-(2-fluorophenyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 195.14 umol, 1 eq) and 6-silaspiro[5.5]undecan-3-amine (35.78 mg, 162.77 umol, 1 *eq*, HCl salt) in DMF (0.5 mL) was added a solution of HOBt (79.10 mg, 585.41 umol, 3 eq) and EDCI (112.22 mg, 585.41 umol, 3 eq) in DMF (0.5 mL), followed by TEA (118.47 mg, 1.17 mmol, 162.96 uL, 6 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed that desired compound was detected. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient:52%-82% over 11min). Compound 5-(2-fluorophenyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (11.1 mg, 25.54 umol, 13.09% yield, 97% purity) was obtained as a white solid.

LCMS m/z 422.1 $[M+1]^+$; ^1H NMR (400MHz, METHANOL-d4) δ = 8.49 (s, 1H), 8.24 (s, 1H), 7.60 - 7.52 (m, 1H), 7.41 (q, J=6.9 Hz, 1H), 7.33 - 7.28 (m, 1H), 7.28 - 7.21 (m, 1H), 7.17 (s, 1H), 3.82 (br t, J=11.1 Hz, 1H), 2.17 (br d, J=12.7 Hz, 2H), 1.80 - 1.63 (m, 6H), 1.46 (br s, 2H), 0.99 (br d, J=13.9 Hz, 2H), 0.83 - 0.76 (m, 2H), 0.74 - 0.64 (m, 4H).

Example 161. MPL-435

Synthesis of 5-(3-pyridyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide



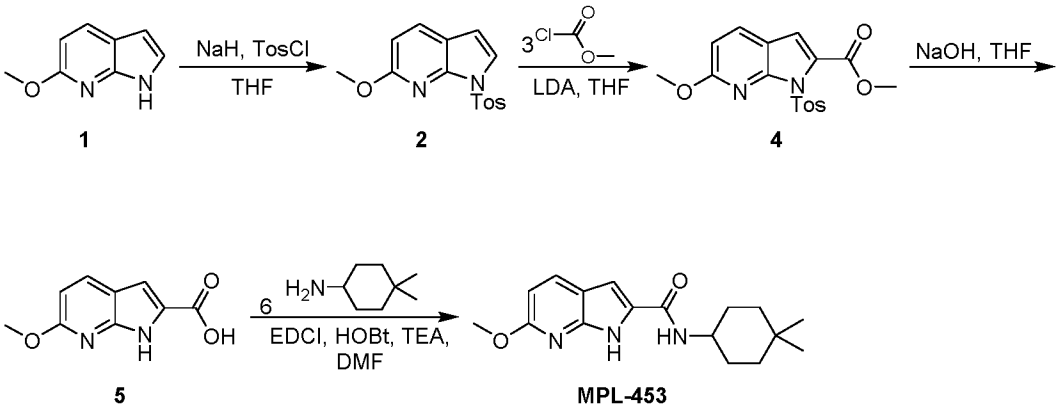
1 **MPL-435**

To a solution of 5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 125.40 umol, 1 eq) (made from 5-bromo-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (200 mg, 560.45 umol) via the same procedures described in Example 158) and 6-silaspiro[5.5]undecan-3-amine (27.57 mg, 125.40 umol, 1 eq, HCl salt) in DMF (0.5 mL) was added a solution of HOBt (50.83 mg, 376.20 umol, 3 eq) and EDCI (72.12 mg, 376.20 umol, 3 eq) in DMF (0.5 mL), followed by TEA (76.13 mg, 752.40 umol, 104.72 uL, 6 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed that desired compound was detected. The reaction mixture was filtered and the filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH3CN; gradient: 45%-75% over 11min). Compound 5-(3-pyridyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (2.9 mg, 7.10 umol, 5.66% yield, 99% purity) was obtained as a white solid.

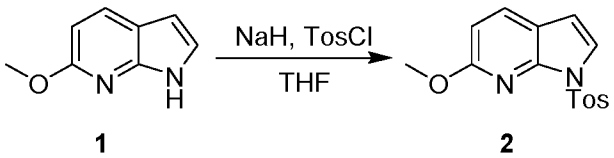
LCMS m/z: 405.2 $[M+1]^+$; ^1H NMR (400MHz, METHANOL-*d*4) δ = 8.87 (s, 1H), 8.63 (d, J=1.8 Hz, 1H), 8.56 (br d, J=4.6 Hz, 1H), 8.38 (d, J=2.0 Hz, 1H), 8.17 (br d, J=8.1 Hz, 1H), 7.57 (dd, J=5.0, 8.0 Hz, 1H), 7.21 (s, 1H), 3.82 (br t, J=11.1 Hz, 1H), 2.17 (br d, J=9.3 Hz, 2H), 1.78 - 1.63 (m, 6H), 1.46 (br s, 2H), 1.31 (t, J=7.4 Hz, 1H), 0.99 (br d, J=14.5 Hz, 2H), 0.83 - 0.74 (m, 2H), 0.73 - 0.63 (m, 4H).

Example 162. MPL-453

Scheme

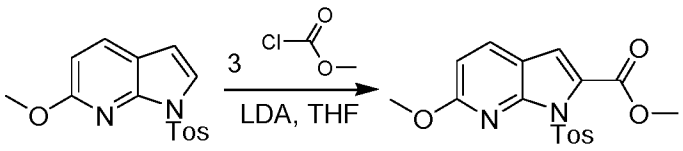


Synthesis of 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine (1 g, 6.75 mmol, 1 eq) in THF (15 mL) was added NaH (404.96 mg, 10.12 mmol, 60% purity, 1.5 eq). The mixture was stirred at 0 °C for 30 mins. TosCl (1.42 g, 7.42 mmol, 1.1 eq) was added. The mixture was stirred at 0 °C for 30 mins. TLC (Petroleum ether : Ethyl acetate = 5:1) indicated starting material was consumed completely and many new spots formed. The reaction was quenched with saturated NH_4Cl (50 mL), then extracted with EtOAc (60 mL x 2). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 5/1). Compound 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.95 g, 5.80 mmol, 86.00% yield, 90% purity) was obtained as a white solid. ^1H NMR was recorded.

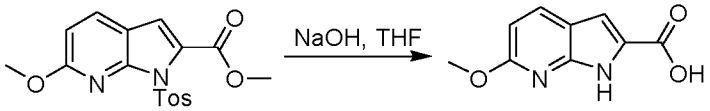
Synthesis of methyl 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate



2 4

To a solution of 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.95 g, 6.45 mmol, 1 eq) in THF (20 mL) was added LDA (2 M in THF, 4.84 mL, 1.5 eq) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 mins. Methyl carbonochloridate (3.05 g, 32.25 mmol, 2.50 mL, 5 eq) (3.720 g) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 mins. TLC (petroleum ether : ethyl acetate = 5:1) indicated new spots formed. The reaction mixture was quenched with saturated NH_4Cl (50 mL), extracted with dichloromethane (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 1/0 to 0/1). Compound methyl 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (372 mg, 929.01 umol, 14.40% yield, 90% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 6-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid



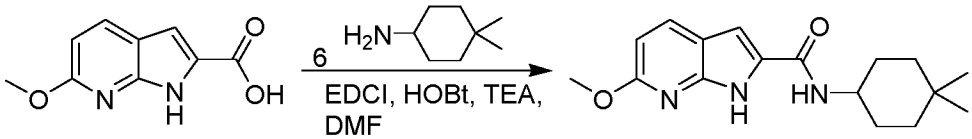
4 5

To a solution of methyl 6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (372 mg, 1.03 mmol, 1 eq) in EtOH (3 mL) was added NaOH (2 M, 2.17 mL, 4.21 eq). The mixture was stirred at 80 °C for 2 hr. TLC (Petroleum ether : Ethyl acetate = 5:1) indicated reactant was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove EtOH. The aqueous phase was adjusted to pH to 3-4 with aqueous HCl (6N) and filtered. The cake was washed with petroleum ether (25 mL), dried under reduced pressure. Compound 6-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid (115 mg, 568.50 umol, 55.08% yield, 95% purity) was obtained as a white solid, which was used for next step without further purification.

^{1}H NMR (400 MHz, DMSO-d6) δ = 12.76 (br s, 1H), 12.15 - 11.93 (m, 1H), 7.95 (d, J=8.7 Hz,

1H), 7.03 (d, J=2.1 Hz, 1H), 6.61 (d, J=8.5 Hz, 1H), 3.94 - 3.87 (m, 3H).

Synthesis of N-(4,4-dimethylcyclohexyl) -6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



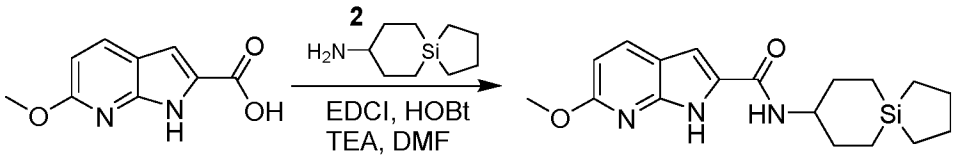
5 **MPL-453**

To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 208.15 umol, 1 eq) and 4,4-dimethylcyclohexanamine (31.78 mg, 249.78 umol, 1.2 eq) in DMF (2 mL) was added a solution of EDCI (119.71 mg, 624.44 umol, 3 eq) and HOBt (84.37 mg, 624.44 umol, 3 eq) in DMF (1 mL), followed by TEA (105.31 mg, 1.04 mmol, 144.86 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired product. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 47%-77%B over 11min). Compound N-(4,4-dimethylcyclohexyl) -6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (43.1 mg, 143.01 umol, 68.70% yield, 100% purity) was obtained as a white solid.

LCMS m/z 302.1 $[M+1]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 11.83 (s, 1H), 8.03 - 7.86 (m, 2H), 7.02 (d, *J*=2.1 Hz, 1H), 6.57 (d, *J*=8.5 Hz, 1H), 3.88 (s, 3H), 3.76 - 3.65 (m, 1H), 1.71 - 1.62 (m, 2H), 1.56 - 1.44 (m, 2H), 1.41 (br d, *J*=12.7 Hz, 2H), 1.32 - 1.21 (m, 2H), 0.93 (d, *J*=10.1 Hz, 6H).

Example 163. MPL-454

Synthesis of 6-methoxy-N-(5-silaspiro [4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



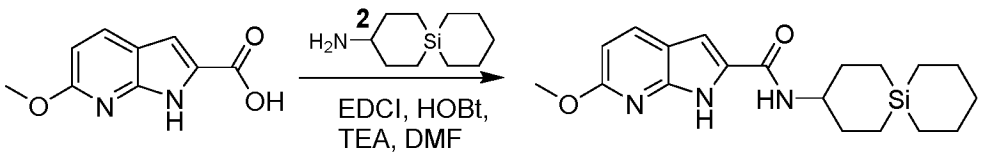
1 **MPL-454**

To a solution of 5-silaspiro[4.5]decan-8-amine (38.55 mg, 187.33 umol, 1.2 eq, HCl salt) and 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 156.11 umol, 1 eq) in DMF (1 mL) was added a solution of EDCI (89.78 mg, 468.33 umol, 3 eq) and HOBt (63.28 mg, 468.33 umol, 3 eq) in DMF (1 mL), followed by TEA (78.98 mg, 780.55 umol, 108.64 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 55%-85%B over 11min). Compound 6-methoxy-N-(5-silaspiro [4.5] decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (24.5 mg, 71.33 umol, 45.69% yield, 100% purity) was obtained as a white solid.

LCMS m/z 344.1 $[M+1]^+$; ^{1}H NMR (500MHz, DMSO-d6) δ = 11.84 (s, 1H), 7.98 (d, J=8.1 Hz, 1H), 7.92 (d, J=8.5 Hz, 1H), 7.02 (d, J=1.8 Hz, 1H), 6.57 (d, J=8.4 Hz, 1H), 3.88 (s, 3H), 3.79 - 3.70 (m, 1H), 2.10 - 2.00 (m, 2H), 1.66 - 1.48 (m, 6H), 0.86 - 0.77 (m, 2H), 0.77 - 0.67 (m, 2H), 0.61 (br t, J=6.7 Hz, 2H), 0.53 (br t, J=6.8 Hz, 2H).

Example 164. MPL-455

Synthesis of 6-methoxy-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



1 MPL-455

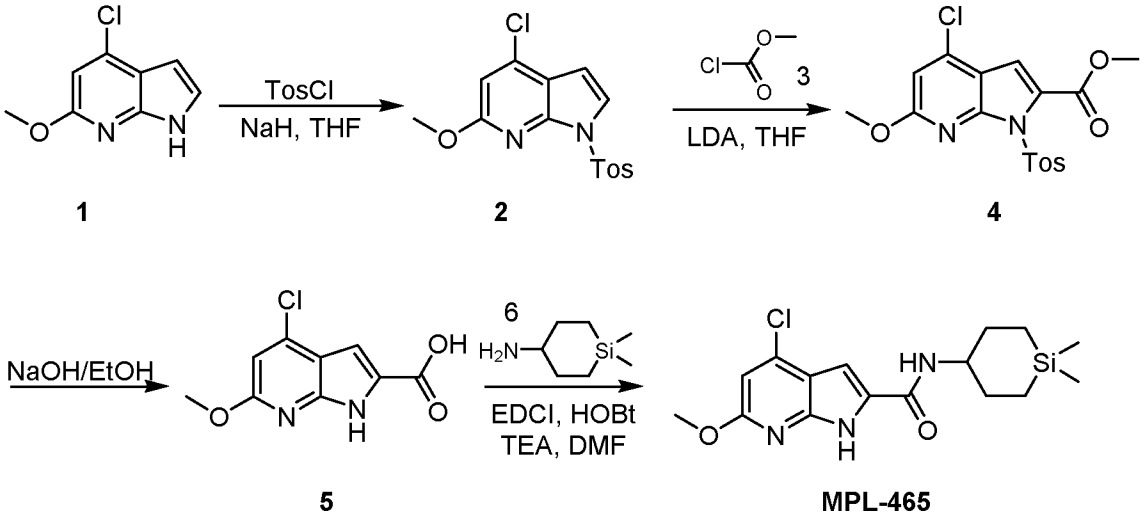
To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 156.11 umol, 1 eq) and 6-silaspiro[5.5]undecan-3-amine (41.18 mg, 187.33 umol, 1.2 eq, HCl salt) in DMF (1 mL) was added a solution of EDCI (89.78 mg, 468.33 umol, 3 eq) and HOBt (63.28 mg, 468.33 umol, 3 eq) in DMF (1 mL), followed by TEA (78.98 mg, 780.55 umol, 108.64 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass was detected. The reaction mixture was filtered. The residue was purified by prep-HPLC (column: Phenomenex Synergi

C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 55%-85%B over 11min). Compound 6-methoxy-N-(6-silaspiro [5.5] undecan-3-yl)-1H-pyrrolo [2,3-b] pyridine-2-carboxamide (48.4 mg, 135.21 umol, 86.61% yield, 99.88% purity) was obtained as a white solid.

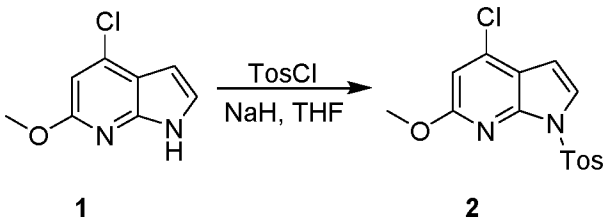
LCMS m/z 358.2 $[M+1]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.84 (s, 1H), 7.97 (d, *J*=8.2 Hz, 1H), 7.92 (d, *J*=8.6 Hz, 1H), 7.01 (d, *J*=2.0 Hz, 1H), 6.57 (d, *J*=8.6 Hz, 1H), 3.88 (s, 3H), 3.76 - 3.64 (m, 1H), 1.99 (br d, *J*=9.8 Hz, 2H), 1.73 - 1.48 (m, 6H), 1.38 (br s, 2H), 0.89 (br d, *J*=14.5 Hz, 2H), 0.74 - 0.65 (m, 2H), 0.63 - 0.51 (m, 4H).

Example 165. MPL-465

Scheme:



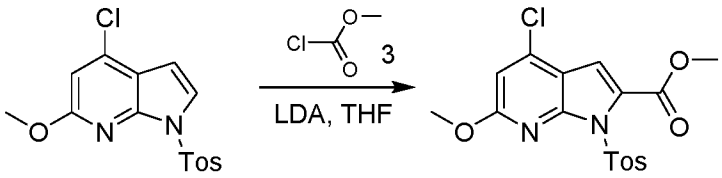
Synthesis of ethyl (Z)-2-azido-3-[2-(2-methoxyethoxy)thiazol-5-yl]prop-2-enoate



To a solution of 4-chloro-6-methoxy-1H-pyrrolo[2,3-b]pyridine (1 g, 5.48 mmol, 1 eq) in THF (20 mL) was added NaH (328.54 mg, 8.21 mmol, 60% purity, 1.5 eq). The mixture was stirred at 0 °C for 30 mins. Then TosCl (1.15 g, 6.02 mmol, 1.1 eq) was added. The mixture was stirred at

0 °C for 30 mins. TLC (Petroleum ether: Ethyl acetate=5:1) indicated starting material was consumed completely and new spot formed. The reaction was quenched with saturated NH_4Cl (50 mL), and then extracted with EtOAc (30 mL x 3). The combined organic layer waswashed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced. The resulting residue was purified by column chromatography (SiO_2, 0-10% Ethyl acetate in petroleum ether). Compound 4-chloro-6-methoxy-1- (p-tolylsulfonyl) pyrrolo[2,3-b]pyridine (1.9 g, 5.08 mmol, 92.72% yield, 90% purity) was obtained as a white solid. ^1H NMR was recorded.

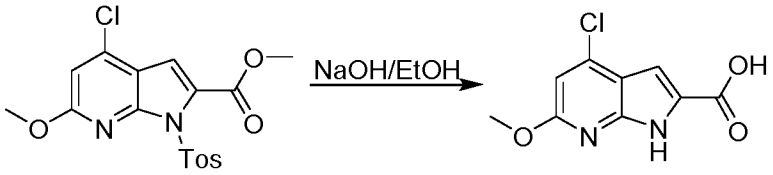
Synthesis of methyl 4-chloro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine-2-carboxylate



2 **4**

To a solution of 4-chloro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.9 g, 5.64 mmol, 1 eq) in THF (20 mL) was added LDA (2 M in THF, 4.23 mL, 1.5 eq) drop-wise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 min. Methyl carbonochloridate (2.67 g, 28.21 mmol, 2.18 mL, 5 eq) (3.200 g) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 mins. TLC (Petroleum ether : Ethyl acetate =5:1) indicated new spots formed. The reaction mixture was quenched with saturated NH_4Cl (50 mL), extracted with dichloromethane (40 mL x 3). The combined organic layer was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-20% Ethyl acetate in petroleum ether). Compound methyl 4-chloro-6-methoxy-1-(p-tolylsulfonyl) pyrrolo [2,3-b]pyridine-2-carboxylate (1.15 g, 2.77 mmol, 49.05% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of 4-chloro-6-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid

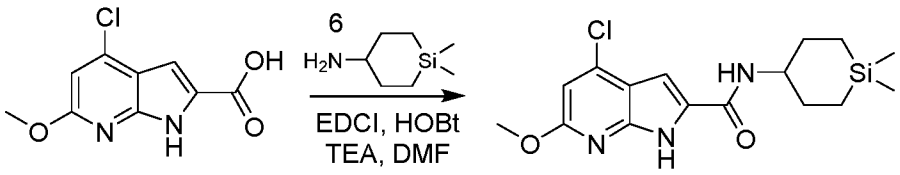


4 5

To a solution of methyl 4-chloro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.15 g, 2.91 mmol, 1 eq) in EtOH (8 mL) was added NaOH (2 M in water, 8 mL, 5.49 eq). The mixture was stirred at 80 °C for 2 hr. TLC (Petroleum ether : Ethyl acetate = 5:1) indicated starting material was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove EtOH. The aqueous phase was adjusted to pH 3-4 with aqueous HCl (6 N), and then filtered. The cake was with petroleum ether (25 mL) and dried under reduced pressure to give 4-chloro-6-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxylic acid (645 mg, 2.56 mmol, 87.95% yield, 90% purity) as a white solid. The crude product was used for the next step without further purification.

^{1}H NMR (400MHz, DMSO-d_6) δ = 12.72 - 12.07 (m, 1H), 6.98 (s, 1H), 6.80 (s, 1H), 3.91 (s, 3H)

Synthesis of 4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



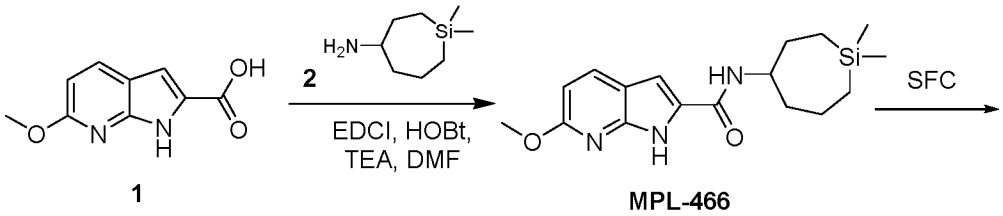
5 MPL-465

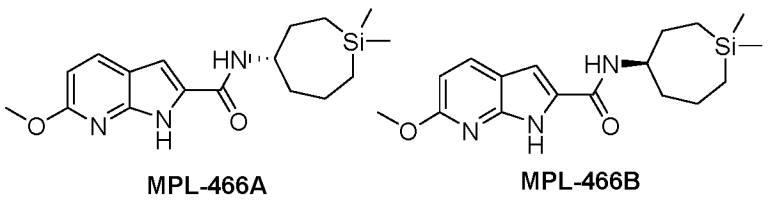
To a solution of 4-chloro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 220.64 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (47.59 mg, 264.77 umol, 1.2 eq, HCl salt) in DMF (1 mL) was added a solution of EDCI (126.89 mg, 661.91 umol, 3 eq) and HOBt (89.44 mg, 661.91 umol, 3 eq) in DMF (1 mL), followed by TEA (111.63 mg, 1.10 mmol, 153.55 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filterate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 60%-90% B over 11 min). Compound 4-chloro-N-(1,1-dimethylsilinan-4-yl) -6-methoxy-1H-

pyrrolo[2,3-b]pyridine-2-carboxamide (59.6 mg, 168.68 umol, 76.45% yield, 99.6% purity) was obtained as a white solid.

LCMS (ESI) m/z: 352.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 12.22 (s, 1H), 8.16 (d, J=7.8 Hz, 1H), 7.14 (s, 1H), 6.75 (s, 1H), 3.89 (s, 3H), 3.76 - 3.63 (m, 1H), 1.98 (br d, J=9.8 Hz, 2H), 1.66 - 1.48 (m, 2H), 0.77 (br d, J=14.5 Hz, 2H), 0.59 (dt, J=4.9, 14.0 Hz, 2H), 0.12 - -0.01 (m, 6H).

Example 166: MPL-466, MPL-466A and MPL-466B





Synthesis of N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide, (S)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide and (R)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide

To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 156.11 umol, 1 eq) and 1,1-dimethylsilepan-4-amine (36.30 mg, 187.33 umol, 1.2 eq, HCl salt) in DMF (1 mL) was added a solution of EDCI (89.78 mg, 468.33 umol, 3 eq) and HOBt (63.28 mg, 468.33 umol, 3 eq) in DMF (1 mL), followed by TEA (78.98 mg, 780.55 umol, 108.64 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient 52%-82% B over 11 min).

Compound N-(1,1-dimethylsilepan-4-yl) -6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide (MPL-466) (25.7 mg, 77.53 umol, 49.66% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 332.2 $[M+H]^+$; ^{1}H NMR (400MHz, DMSO-d6) δ = 11.83 (s, 1H), 8.00 (d, *J*=7.8 Hz, 1H), 7.92 (d, *J*=8.6 Hz, 1H), 7.02 (d, *J*=1.7 Hz, 1H), 6.57 (d, *J*=8.6 Hz, 1H), 3.88 (s, 4H), 1.97 - 1.74 (m, 3H), 1.72 - 1.60 (m, 1H), 1.56 - 1.42 (m, 2H), 0.81 - 0.68 (m, 2H), 0.67 - 0.54 (m, 2H), 0.03 (d, *J*=6.4 Hz, 6H).

The above reaction was conducted at a larger scale from 624.44 umol of compound 1, which was made using the same procedures described for the synthesis of compound 5 from compound 1 in Example 153. The racemic MPL-466 isolated from prep-HPLC was separated by SFC (Berger MG II, column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: A: 0.1%NH_3H_2O in MeOH; B: CO_2; isocratic 40%B; flow rate: 80 mL/min) to afford two peaks (two enantiomers), (S)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy- 1H-pyrrolo[2,3-b]pyridine-2-carboxamide and (R)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H- pyrrolo[2,3-b]pyridine-2-carboxamide.

Peak1 (MPL-466A): 82.8 mg, 249.79 umol, 33.12% yield, 100% purity, a white solid.

LCMS m/z: 332.1 $[M+1]^+$; ^{1}H NMR (400MHz, DMSO-d6) δ = 11.84 (s, 1H), 8.00 (d, J=7.8 Hz, 1H), 7.92 (d, J=8.6 Hz, 1H), 7.02 (d, J=2.0 Hz, 1H), 6.57 (d, J=8.2 Hz, 1H), 3.88 (s, 4H), 1.96 - 1.75 (m, 3H), 1.72 - 1.60 (m, 1H), 1.56 - 1.41 (m, 2H), 0.82 - 0.68 (m, 2H), 0.67 - 0.55 (m, 2H), 0.03 (d, J=6.3 Hz, 6H).

Peak 2 (MPL-466B): 92.4 mg, 277.64 umol, 36.81% yield, 99.60% purity, a white solid.

MPL-466A and MPL-466B were also analyzed by analytical SFC.

Conditions:

Instrument: CAS-SH-ANA-SFC-K (Waters UPCC with PDA Detector)

Column: Chiralpak AD-3 50*4.6mm, 3um particle size

Mobile phase: A: CO_2, B: 0.05% DEA in methanol

Isocratic: 40% B

Flow rate: 2.5mL/min

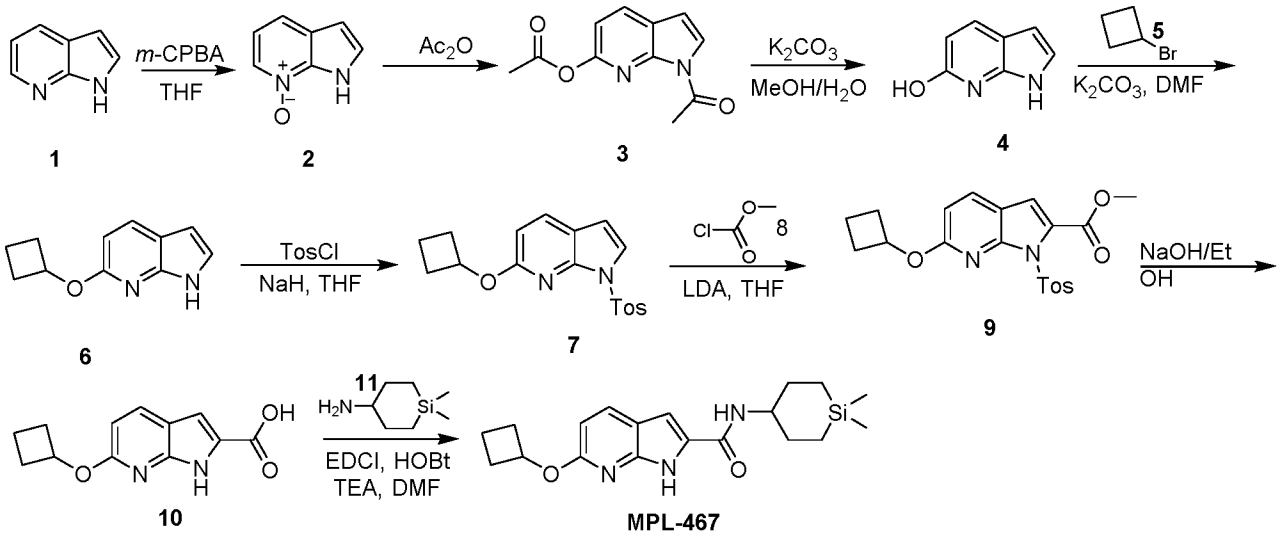
Column temp.: 35 °C

ABPR: 1500 psi

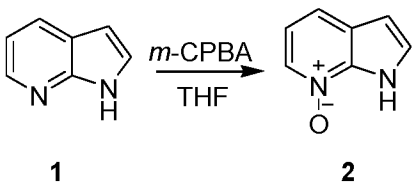
MPL-466A: retention time 2.53 min; 100% ee; MPL-466B: retention time: 3.55min; 100% ee.

Example 167. MPL-467

Scheme



Synthesis of 7-oxido-1H-pyrrolo

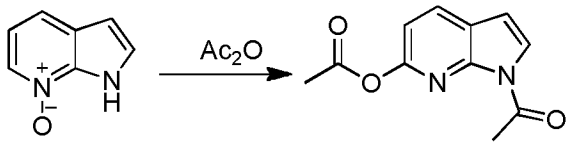


To a solution of 1H-pyrrolo[2,3-b]pyridine (9 g, 76.18 mmol, 1 eq) in THF (100 mL) was added 3-chlorobenzenecarboperoxoic acid (23.20 g, 114.28 mmol, 85% purity, 1.5 eq). The mixture was stirred at 25 °C for 12 hr. LC-MS showed desired mass was detected. The reaction mixture was diluted with Petroleum ether (200 mL), filtered and concentrated under reduced pressure afford 7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (19 g, 70.82 mmol, 92.97% yield, 50% purity) as

a white solid. The crude product was used in next step without further purification.

LCMS (ESI) m/z: 267.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of (1-acetylpyrrolo[2,3-b]pyridin-6-yl) acetate

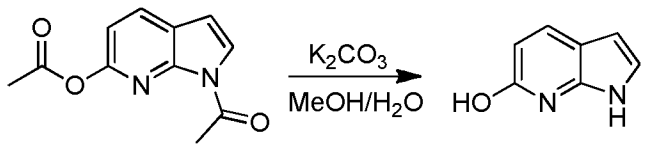


2 3

A mixture of 7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (20 g, 74.55 mmol, 50% purity, 1 eq) in Ac_2O (107.39 g, 1.05 mol, 98.52 mL, 14.11 eq) was stirred at 140 °C for 12 hr. LC-MS showed desired mass. The reaction mixture was concentrated to half volume, and then extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was washed with H_2O (100 x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-20% Ethyl acetate in petroleum ether). Compound (1-acetylpyrrolo[2,3-b]pyridin-6-yl) acetate (18 g, crude) was obtained as a white solid.

LCMS (ESI) m/z: 219.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 1H-pyrrolo[2,3-b]pyridin-6-ol

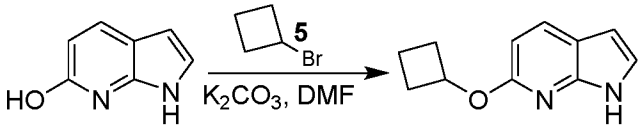


3 4

To a solution of (1-acetylpyrrolo[2,3-b]pyridin-6-yl) acetate (17 g, 77.91 mmol, 1 eq) in MeOH (30 mL) and H_2O (30 mL) was added K_2CO_3 (32.30 g, 233.72 mmol, 3 eq). The mixture was stirred at 25 °C for 12 hr. LC-MS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove MeOH, and then filtered. The cake was dried under reduced pressure. Compound 1H-pyrrolo[2,3-b]pyridin-6-ol (6 g, crude) was obtained as a brown solid.

LCMS (ESI) m/z: 135.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-(cyclobutoxy)-1H-pyrrolo [2,3-b]pyridine

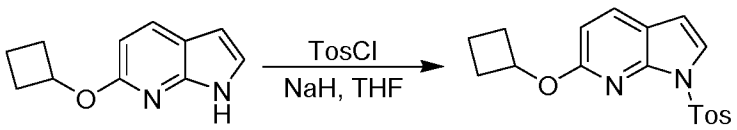


4 6

To a solution of 1H-pyrrolo[2,3-b]pyridin-6-ol (2 g, 14.91 mmol, 1 eq) in DMF (20 mL)was added bromocyclobutane (2.42 g, 17.89 mmol, 1.69 mL, 1.2 eq) and K_2CO_3 (2.06 g, 14.91 mmol, 1 eq). The mixture was stirred at 80 °C for 12 hr. LC-MS showed desired mass. The residue was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer waswashed with H2O (30 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-10% Ethyl acetate in petroleum ether). Compound 6-(cyclobutoxy)-1H-pyrrolo [2,3-b]pyridine (400 mg, 1.91 mmol, 12.83% yield, 90% purity) was obtained as a white solid.

LCMS (ESI) m/z: 189.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-(cyclobutoxy)-1- (p-tolylsulfonyl) pyrrolo[2,3-b]pyridine

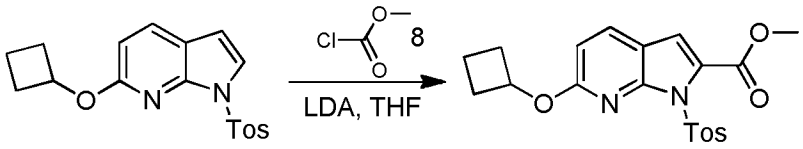


6 7

To a solution of 6-(cyclobutoxy)-1H-pyrrolo[2,3-b]pyridine (446 mg, 2.37 mmol, 1 eq) in THF (10 mL) was added NaH (142.16 mg, 3.55 mmol, 60% purity, 1.5 eq). The mixture was stirred at 0 °C for 30 mins. Then TosCl (496.91 mg, 2.61 mmol, 1.1 eq) was added. The mixture was stirred at 0 °C for 30 mins. TLC (Petroleum ether : Ethyl acetate=5:1) indicated starting material was consumed completely and new spot formed. The reaction was quenched with saturated NH_4Cl (30 mL), and then extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-10% Ethyl acetate in petroleum ether1). Compound 6-(cyclobutoxy)-1- (p-tolylsulfonyl) pyrrolo[2,3-

b]pyridine (680 mg, 1.79 mmol, 75.43% yield, 90% purity) was obtained as a white solid. ^{1}H NMR was recorded.

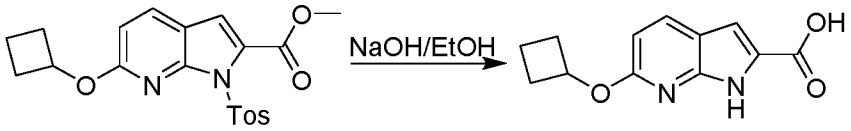
Synthesis of methyl 6-(cyclobutoxy)-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine-2-carboxylate



7 **9**

To a solution of 6-(cyclobutoxy)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (680 mg, 1.99 mmol, 1 eq) in THF (12 mL) was added LDA (2 M in THF, 1.49 mL, 1.5 eq) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 mins. Methyl carbonochloridate (938.31 mg, 9.93 mmol, 769.11 uL, 5 eq) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 mins. TLC (Petroleum ether : Ethyl acetate=5:1) indicated new spots formed. The reaction mixture was quenched with saturated NH_4Cl (30 mL), and then extracted with dichloromethane (40 mL x 3). The combined organic layer was washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-20% Ethyl acetate in petroleum ether). Compound methyl 6-(cyclobutoxy)-1-(p-tolylsulfonyl) pyrrolo [2,3-b]pyridine-2-carboxylate (245 mg, 550.63 umol, 27.73% yield, 90% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 6-(cyclobutoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylicacid



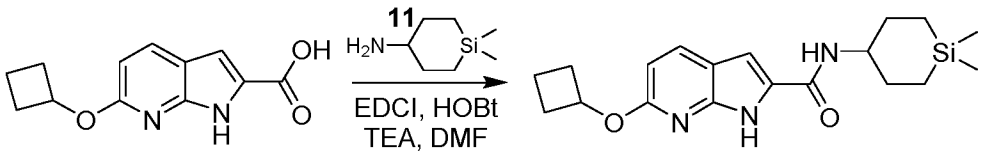
9 **10**

To a solution of methyl 6-(cyclobutoxy)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (1.17 g, 2.91 mmol, 1 eq) in EtOH (4 mL) was added NaOH (2 M in water, 4 mL, 2.75 eq). The mixture was stirred at 80 °C for 2 hr. TLC (Petroleum ether : Ethyl acetate=5:1) indicated starting material was consumed completely and one new spot formed.The reaction mixture was concentrated under reduced pressure to remove EtOH. The aqueous phase was adjust to pH 3-4

with aqueous HCl (6 N), and filtered. The cake was washed with petroleum ether (25 mL) and dried under reduced pressure. Compound 6-(cyclobutoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (145 mg, 561.93 umol, 19.29% yield, 90% purity) was obtained as a white solid. The crude product was used for the next step without further purification.

^{1}H NMR (500MHz, DMSO-d_6) δ = 13.38 - 12.28 (m, 1H), 12.07 - 11.83 (m, 1H), 7.94 (d, *J*=8.5 Hz, 1H), 7.01 (d, *J*=2.1 Hz, 1H), 6.56 (d, *J*=8.5 Hz, 1H), 5.17 (quin, *J*=7.3 Hz, 1H), 2.47 - 2.39 (m, 2H), 2.12 - 2.01 (m, 2H), 1.85 - 1.74 (m, 1H), 1.71 - 1.58 (m, 1H).

Synthesis of 6-(cyclobutoxy)-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



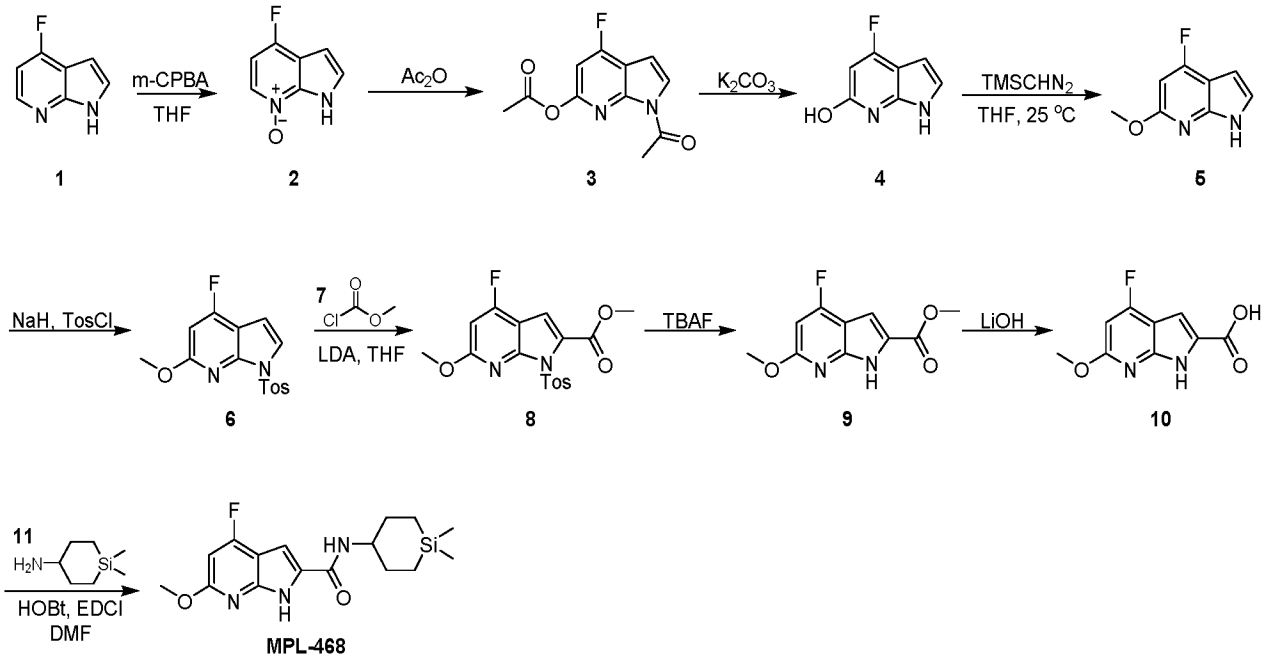
10 **MPL-467**

To a solution of 6-(cyclobutoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 215.30 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (46.44 mg, 258.36 umol, 1.2 eq, HCl salt) in DMF (1 mL) was added a solution of EDCI (123.82 mg, 645.90 umol, 3 eq) and HOBt (87.28 mg, 645.90 umol, 3 eq) in DMF (1 mL), followed by TEA (108.93 mg, 1.08 mmol, 149.83 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 58%-88% B over 11 min). Compound 6-(cyclobutoxy)-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo [2,3-b] pyridine-2-carboxamide (52.5 mg, 146.84 umol, 68.20% yield, 100% purity) was obtained as a white solid.

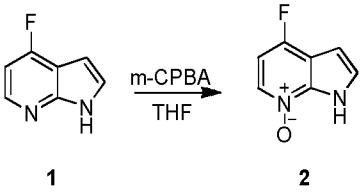
LCMS (ESI) m/z: 358.3 $[M+H]^+$; ^{1}1H NMR (500MHz, DMSO-d6) δ = 11.72 (s, 1H), 8.04 - 7.81 (m, 2H), 6.99 (d, *J*=2.0 Hz, 1H), 6.52 (d, *J*=8.5 Hz, 1H), 5.15 (quin, *J*=7.2 Hz, 1H), 3.75 - 3.63 (m, 1H), 2.48 - 2.38 (m, 2H), 2.12 - 1.93 (m, 4H), 1.79 (q, *J*=10.2 Hz, 1H), 1.71 - 1.50 (m, 3H), 0.77 (br d, *J*=14.5 Hz, 2H), 0.60 (dt, *J*=4.7, 14.0 Hz, 2H), 0.13 - 0.00 (m, 6H).

Example 168: MPL-468

Scheme

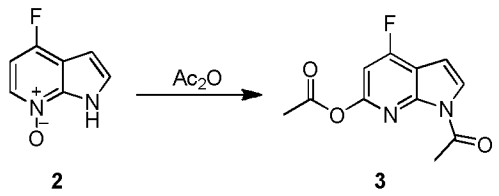


Synthesis of 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium



To a solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridine (10 g, 73.46 mmol, 1 *eq*) in THF (150 mL) was added m-CPBA (18.22 g, 84.48 mmol, 80% purity, 1.15 *eq*) in batches. The mixture was stirred at 20 °C for 12 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely. The reaction mixture was poured into petroleum ether (500 mL), precipitates were collected by filtration. The cake was washed with petroleum ether (50 mL x 2). The filtrate was quenched with Na_2SO_3 (Sat. 200 mL) and discarded. Compound 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (20.2 g, 66.39 mmol, 90.38% yield, 50% purity) was obtained as a white solid. ^1H NMR was recorded.

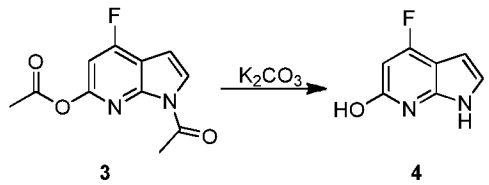
Synthesis of (1-acetyl-4-fluoro-pyrrolo[2,3-b]pyridin-6-yl) acetate



2 3

A solution of 4-fluoro-7-oxido-1H-pyrrolo[2,3-b]pyridin-7-ium (16 g, 52.59 mmol, 50% purity, 1 *eq*) in acetyl acetate (130.80 g, 1.28 mol, 120.00 mL, 24.36 *eq*) was stirred at 60 °C for 10 min. LCMS showed starting material was consumed completely and desired mass was detected. TLC (Petroleum ether : EtOAc = 10:1) showed one major spot. The mixture was concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, 0-10% Ethyl acetate in petroleum ether at 100 mL/min). Compound (1-acetyl-4-fluoro-pyrrolo[2,3-b]pyridin-6-yl) acetate (13.2 g, 16.77 mmol, 31.88% yield, 30% purity) was obtained as a colorless oil. ^{1}H NMR was recorded.

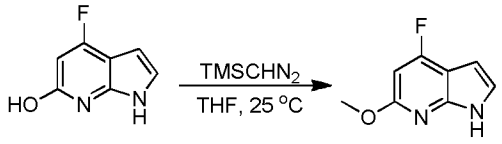
Synthesis of 4-fluoro-1H-pyrrolo[2,3-b]pyridin-6-ol



3 4

To a solution of (1-acetyl-4-fluoro-pyrrolo[2,3-b]pyridin-6-yl) acetate (13 g, 16.51 mmol, 30% purity, 1 *eq*) in MeOH (150 mL) and H_2O (50 mL) was added K_2CO_3 (9.13 g, 66.05 mmol, 4 *eq*). The mixture was stirred at 25 °C for 12 hr. LCMS showed starting material was consumed completely, and one peak with desired mass was detected. The reaction was quenched by dropwise addition of aqueous HCl (12 N) until pH = 1. The mixture was diluted with H_2O (700 mL) to a solution, and then extracted by EtOAc (120 mL x 5). The combined filtrate was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was diluted with CH_3CN (10 mL) and water (40 mL), sonicated for 15 min and then filtered. The filter cake was dried under reduced pressure to afford crude compound 4 (1.5 g, 6.90 mmol, 41.80% yield, purity 70% purity) as a white solid. Additional amount of compound 4 (800 mg, 4.73 mmol, 28.66% yield, 90% purity) was obtained as a white solid after lyophilization of the filtrate. ^{1}H NMR was recorded.

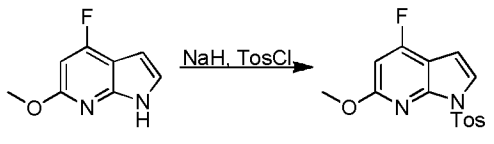
Synthesis of 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine



4 5

To a salt-ice cooled solution of 4-fluoro-1H-pyrrolo[2,3-b]pyridin-6-ol (1.4 g, 9.20 mmol, 1 *eq*) (from above 1.5g of compound 4) in THF (150 mL) was added $TMSCHN_2$ (2 M in ether, 6.90 mL, 1.5 *eq*) dropwise and stirred at 50 °C for 6 hr under N_2. LCMS showed the starting material remained. The mixture was stirred at 50 °C for additional 12 h. $TMSCHN_2$ (2M in ether, 7 mL) was added and the mixture was stirred at 50 °C for another 8 h. LCMS showed the starting material remained. The mixture was stirred at 50 °C for another 12 h. LCMS showed the starting material remained. Additional $TMSCHN_2$ (2M in ether, 7 mL) was added. The mixture was stirred at 50 °C for another 8 h. LCMS showed one main peak with desired mass. The mixture was poured into saturated NH_4Cl (150 mL), and then extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0~20% Ethyl acetate in petroleum ether at 40 mL/min). Compound 4-fluoro-6-methoxy- 1H-pyrrolo[2,3-b]pyridine (900 mg, 5.15 mmol, 55.92% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine

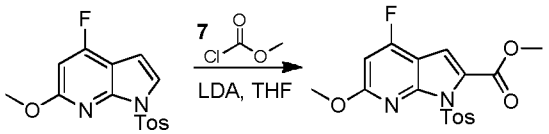


5 6

To an ice-cooled solution of 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine (900 mg, 5.42 mmol, 1 *eq*) in THF (15 mL) was added NaH (281.64 mg, 7.04 mmol, 60% purity, 1.3 *eq*) in batches, the mixture was stirred at 0 °C for 0.5 h. Then TosCl (1.14 g, 5.96 mmol, 1.1 *eq*) was added. The mixture was stirred at 0 °C for 0.5 hr. TLC (Petroleum ether : EtOAc = 10:1) showed starting material was consumed completely, and one new spot formed. The reaction mixture was

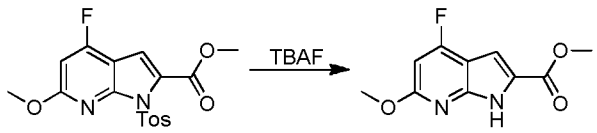
poured into saturated NH_4Cl (40 mL), and then extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, eluent of 0-10% ethyl acetate in petroleum ether at 40 mL/min). Compound 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (1.65 g, 4.89 mmol, 90.34% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of methyl 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine-2-carboxylate



To a solution of 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (500 mg, 1.56 mmol, 1 *eq*) in THF (10 mL) (dried by Na and distilled) was added LDA (2 M in THF, 1.17 mL, 1.5 *eq*) dropwsie at -70 °C under N_2. The mixture was stirred at -70 ~ -60 °C for 1h. Methyl carbonochloridate (302.37 mg, 3.20 mmol, 247.84 uL, 2.05 *eq*) was added dropwise, the mixture was stirred at -70 °C for 1 hr. TLC (Petroleum ether : EtOAc = 10:1) showed starting material was consumed completely, one new spot formed. The mixture was poured into saturated NH_4Cl (30 mL), and extracted with EtOAc (15 mL x 2). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (ISCO®; 12 SepaFlash® Silica Flash Column, Eluent of 0~15% ethyl acetate in petroleum ether at 40 mL/min). Compound methyl 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (320 mg, 803.44 umol, 51.47% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

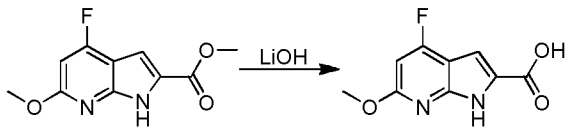
Synthesis of methyl 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate



8 9

To a solution of methyl 4-fluoro-6-methoxy-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (320 mg, 845.72 umol, 1 *eq*) in THF (5 mL) was added TBAF (1 M in THF, 1.01 mL, 1.2 *eq*). The mixture was stirred at 25 °C for 12 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely, and one new spot formed. The mixture was concentrated under reduced pressure. The resulting residue was diluted with water (10 mL) and sonicated for 15 min and filtered. The cake was washed with water (5 mL). Compound methyl 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (190 mg, crude) was obtained as a white solid. It was used for the next step without further purification.

Synthesis of 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

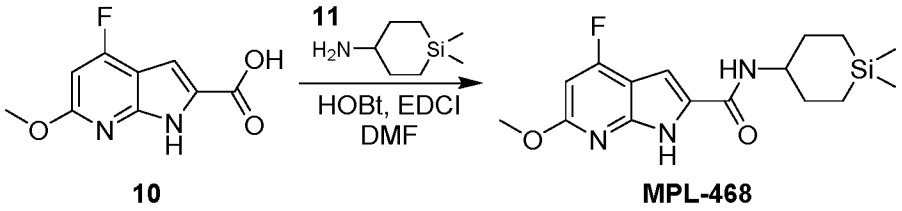


9 10

To a solution of methyl 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (190 mg, 847.50 umol, 1 *eq*) in THF (3 mL) was added a solution of $LiOH.H_2O$ (284.51 mg, 6.78 mmol, 8 *eq*) in H_2O (3 mL). The mixture was stirred at 25 °C for 2 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely, one new spot formed. The mixture was concentrated under reduced pressure. The aqueous residue was diluted with H_2O (5 mL), aqueous HCl (6 N) was added until pH to 3, and then filtered. The filtrate was concentrated by lyophilization. Compound 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (195 mg, 835.07 umol, 98.53% yield, 90% purity).

^{1}H NMR (400 MHz, DMSO-d_6) δ =13.02 (br s, 1H), 12.45 (br s, 1H), 7.03 (d, *J*=1.8 Hz, 1H), 6.51 (d, *J*=11.3 Hz, 1H), 3.91 (s, 3H)

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



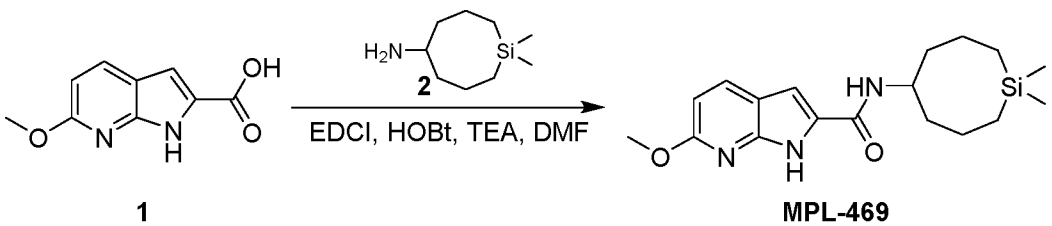
10 MPL-468

To a solution of 4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (50 mg, 237.91 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (47.04 mg, 261.70 umol, 1.1 *eq*, HCl salt) in DMF (1 mL) was added a solution of HOBt (64.29 mg, 475.82 umol, 2 *eq*) and EDCI (91.22 mg, 475.82 umol, 2 *eq*) in DMF (1 mL), followed by TEA (96.30 mg, 951.65 umol, 132.46 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed starting material was consumed completely, and one major peak with desired mass was detected. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: Welch Xtimate 75*40mm*3um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 55%-85% B over 10 min). Compound N-(1,1-dimethylsilinan-4-yl)-4- fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (32 mg, 95.39 umol, 40.10% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 336.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ = 12.20 (br s, 1H), 8.08 (d, *J*=8.1 Hz, 1H), 7.11 (s, 1H), 6.47 (d, *J*=11.3 Hz, 1H), 3.89 (s, 3H), 3.75 - 3.61 (m, 1H), 2.04 - 1.91 (m, 2H), 1.64 - 1.50 (m, 2H), 0.77 (br d, *J*=14.6 Hz, 2H), 0.59 (dt, *J*=4.8, 13.9 Hz, 2H), 0.12 - 0.02 (m, 6H).

Example 169. MPL-469

Synthesis of N-(1,1-dimethylsilocan-5-yl)-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide



1 MPL-469

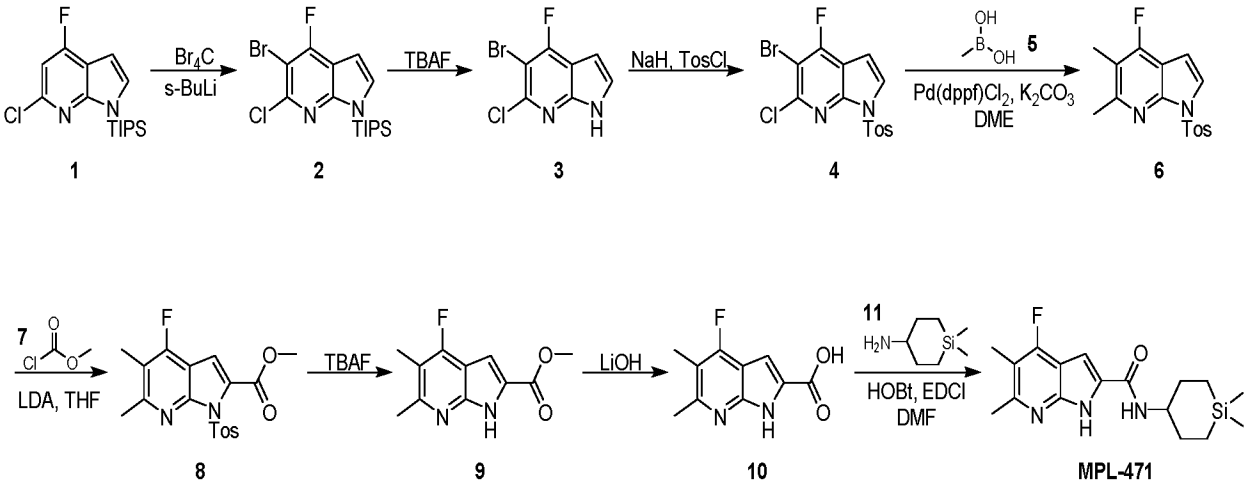
To a solution of 6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (40 mg, 208.15 umol, 1

eq) and 1,1-dimethylsilocan-5-amine (51.91 mg, 249.78 umol, 1.2 eq, HCl salt) in DMF (1 mL) was added a solution of EDCI (119.71 mg, 624.44 umol, 3 eq) and HOBt (84.38 mg, 624.44 umol, 3 eq) in DMF (1 mL), followed by TEA (105.31 mg, 1.04 mmol, 144.86 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The residue was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 60%-90% B over 11 min). The residue from prep-HPLC was further purified by SFC (Instrument: Berger MG II; column: DAICEL CHIRALPAK AS (250mm*30mm,10um); mobile phase: A: 0.1%NH_3H_2O in EtOH; B CO_2, isocratic 30%B). Compound N-(1,1-dimethylsilocan-5-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (7 mg, 20.26 umol, 35.00% yield, 100% purity) was obtained as a white solid.

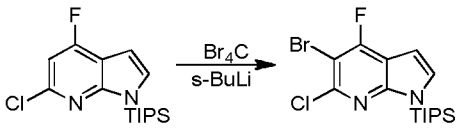
LCMS (ESI) m/z: 346.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.80 (s, 1H), 8.05 (d, J=8.1 Hz, 1H), 7.92 (d, J=8.6 Hz, 1H), 7.02 (d, J=1.7 Hz, 1H), 6.57 (d, J=8.6 Hz, 1H), 4.08 - 3.96 (m, 1H), 3.88 (s, 3H), 1.73 - 1.57 (m, 8H), 0.80 - 0.64 (m, 4H), 0.03 (d, J=18.8 Hz, 6H).

Example 170. MPL-471

Scheme



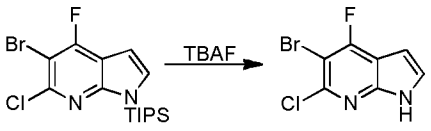
Synthesis of (5-bromo-6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane



1 2

To a solution of (6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (9 g, 27.53 mmol, 1 *eq*) in THF (270 mL) was added n-BuLi (2.5 M in n-hexane, 22.02 mL, 2 *eq*) dropwise under N_2 at -78 °C. The mixture was stirred at -70 °C ~ - 60 °C for 1 hr. Then a solution of carbon tetrabromide (22.82 g, 68.83 mmol, 2.5 *eq*) in THF (30 mL) was added dropwise. The reaction mixture was stirred at -70 °C ~ - 60 °C for 1 hr. LC-MS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was poured into saturated NH_4Cl (700 mL), and extacted with EtOAc (200 mL x 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column; 0-3% ethyl acetate in petroleum ether at 100 mL/min). Compound (5-bromo-6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (15 g, 25.87 mmol, 93.98% yield, 70% purity) was obtained as a light yellow oil. ^1H NMR was recorded.

Synthesis of 5-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine



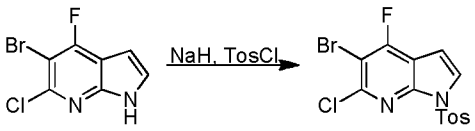
2 3

To a solution of (5-bromo-6-chloro-4-fluoro-pyrrolo[2,3-b]pyridin-1-yl)-triisopropyl-silane (16 g, 39.43 mmol, 1 *eq*) in THF (20 mL) was added TBAF (1 M in THF, 47.31 mL, 1.2 *eq*). The mixture was stirred at 20 °C for 3 hr. LCMS showed starting material was consumed completely, and one major peak with desired mass was detected. The mixture was poured into water (700 mL) with stirring, and then extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine (100 mL), dried by Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was diluted with a mixture of petroleum ether/ EtOAc (20 : 1, 100 mL) and sonicated for 15 min before filtration. The cake was washed with petroleum ether/EtOAc (10:1,

20 mL x 2) and dried to afford 5-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (3.1 g, 11.18 mmol, 28.37% yield, 90% purity) as a yellow solid. ^{1}H NMR was recorded.

The combined filtrate was concentrated under reduced pressure, the resulting residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent 0-40% ethyl acetate in petroleum ether at 50 mL/min) to afford additional amount of desire product (0.9 g, 3.43 mmol, 8.69% yield, 95% purity) as a yellow solid. ^{1}H NMR was recorded.

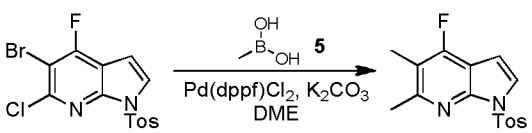
Synthesis of 5-bromo-6-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



3 4

To an ice-cooled solution of 5-bromo-6-chloro-4-fluoro-1H-pyrrolo[2,3-b]pyridine (500 mg, 2.00 mmol, 1 *eq*) in THF (10 mL) was added NaH (120.24 mg, 3.01 mmol, 60% purity, 1.5 *eq*) at 0 °C in batches. The mixture was stirred at 0 °C for 0.5 hr. TosCl (458.53 mg, 2.41 mmol, 1.2 *eq*) was added. The mixture was stirred at 0 °C for 0.5 hr. TLC (Petroleum ether : EtOAc = 10:1) showed starting material was consumed completely and one new spot formed. The mixture was poured into saturated NH_4Cl (30 mL), and then extracted with EtOAc (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 20 SepaFlash® Silica Flash Column, Eluent of 0-5% ethyl acetate in petroleum ether at 50 mL/min). Compound 5-bromo-6-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo [2,3-b]pyridine (450 mg, 1.06 mmol, 52.84% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

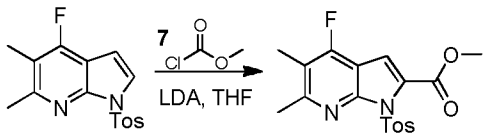
Synthesis of 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



4 6

To a mixture of 5-bromo-6-chloro-4-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (300 mg, 743.21 umol, 1 *eq*), $MeB(OH)_2$ (444.89 mg, 7.43 mmol, 10 *eq*) and K_2CO_3 (308.15 mg, 2.23 mmol, 3 *eq*) was added DME (20 mL). The mixture was purged with N_2 and then $Pd(dppf)Cl_2.CH_2Cl_2$ (121.39 mg, 148.64 umol, 0.2 *eq*) was added under N_2. The mixture was stirred at 110 °C for 12 hr under N_2. TLC (Petroleum ether : EtOAc = 10:1) showed starting material was consumed completely, and one new spot with desired mass was detected. The mixture was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent 0-10% ethyl acetate in petroleum ether at 25 mL/min). Compound 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (270 mg, 720.87 umol, 96.99% yield, 85% purity) was obtained as a white solid. ^1H NMR was recorded.

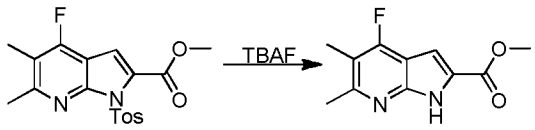
Synthesis of methyl 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b] pyridine-2-carboxylate



6 8

To a solution of 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (270 mg, 848.08 umol, 1 *eq*) in THF (5 mL) (dried by Na and distilled) was added LDA (2 M in THF, 636.06 uL, 1.5 *eq*) dropwise at -70 °C under N_2. After stirring at -70 °C ~ -60 °C for 1 hr, methyl carbonochloridate (240.42 mg, 2.54 mmol, 197.07 uL, 3 *eq*) was added dropwise. The mixture was stirred at -70 ~ -60 °C for 1 hr. TLC (Petroleum ether : EtOAc = 10:1) showed a little starting material remained and one major new spot formed. The mixture was poured into saturated NH_4Cl (25 mL), and then extracted by EtOAc (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent 0-15% ethyl acetate in petroleum ether at 25 mL/min). Compound methyl 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine- 2-carboxylate (180 mg, 454.30 umol, 53.57% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

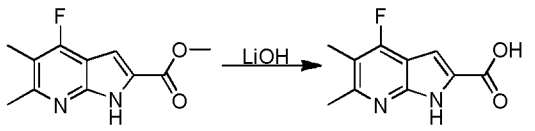
Synthesis of methyl 4-fluoro-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate



8 9

To a solution of methyl 4-fluoro-5,6-dimethyl-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine-2-carboxylate (180 mg, 478.21 umol, 1 *eq*) in THF (2 mL) was added TBAF (1 M in THF, 526.03 uL, 1.1 *eq*). The mixture was stirred at 25 °C for 2 hr. TLC (Petroleum ether : EtOAc = 10:1) showed starting material was consumed completely, one major new spot formed. The mixture was concentrated under reduced pressure. The resulting residue was diluted with water (5 mL) and sonicated for 15 min before filtration. The cake was collected and washed with H_2O (2 mL). Compound methyl 4-fluoro-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (100 mg, crude) was obtained as a brown solid.

Synthesis of 4-fluoro-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid

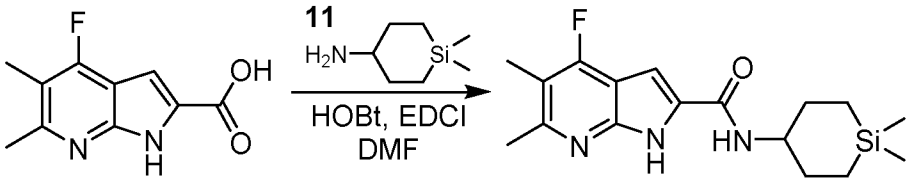


9 10

To a solution of methyl 4-fluoro-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (100 mg, 450.01 umol, 1 *eq*) in THF (2 mL) and H_2O (2 mL) was added $LiOH.H_2O$ (169.96 mg, 4.05 mmol, 9 *eq*). The mixture was stirred at 25 °C for 12 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely, and one new spot formed. The mixture was concentrated under reduced pressure to remove THF. The pH of aqueous phase was adjusted to 3 with aqueous HCl (6 N). The solid was collected by filtration. Compound 4-fluoro-5,6-dimethyl-1H- pyrrolo[2,3-b]pyridine-2-carboxylic acid (100 mg, 432.30 umol, 96.06% yield, 90% purity) was obtained as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.30 (br s, 1H), 6.98 (s, 1H), 2.53 (s, 3H), 2.22 (s, 3H)

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5,6-dimethyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide

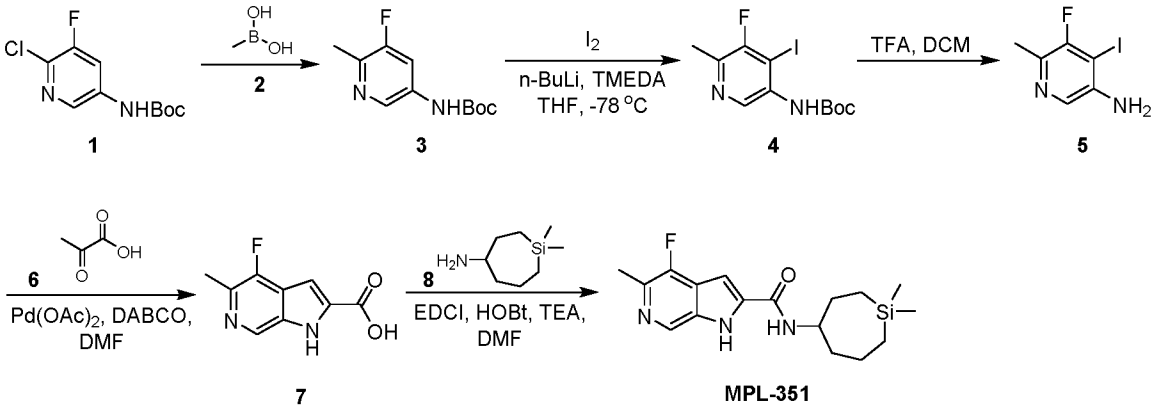


10 **MPL-471**

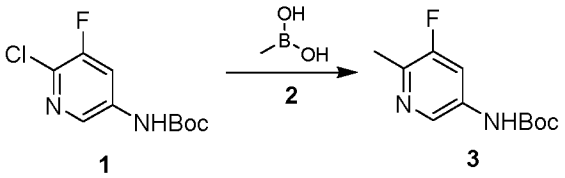
To a solution of 4-fluoro-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (30 mg, 144.10 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (31.08 mg, 172.92 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (55.25 mg, 288.20 umol, 2 *eq*) and HOBt (38.94 mg, 288.20 umol, 2 *eq*) in DMF (1 mL), followed by TEA (58.33 mg, 576.40 umol, 80.23 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed starting material was consumed completely, and one major peak with desired mass was detected. The reaction was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (colum: Phenomenex luna C18 100*40mm*3 um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 55%-85% B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5,6- dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (20 mg, 59.97 umol, 50.00% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 334.3 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ = 12.06 (br s, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 7.10 (s, 1H), 3.76 - 3.62 (m, 1H), 2.50 (s, 3H), 2.21 (d, *J*=1.1 Hz, 3H), 2.05 - 1.91 (m, 2H), 1.66 - 1.51 (m, 2H), 0.77 (br d, *J*=14.5 Hz, 2H), 0.59 (dt, *J*=4.8, 14.1 Hz, 2H), 0.13 - -0.03 (m, 6H).

Example 171. MPL-351



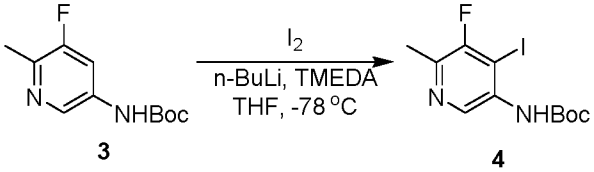
Synthesis of tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate



A mixture of tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (1.8 g, 7.30 mmol, 1 *eq*), methylboronic acid (2.18 g, 36.49 mmol, 5 *eq*) and Cs_2CO_3 (7.13 g, 21.89 mmol, 3 *eq*) in H_2O (0.1 mL) and dioxane (10 mL) was de-gassed and $Pd(dppf)Cl_2$ (533.95 mg, 729.73 umol, 0.1 *eq*) was then added. The mixture was heated at 100 °C for 12 hours under N_2. LC-MS indicated desired mass. The reaction mixture was diluted with EtOAc (30 mL) and filtered to remove the insoluble material. The filtrate was concentrated in vacuo. The residue was purified by flash silica gel chromatography (SiO_2, 0-30% ethyl acetate in petroleum ether). Compound tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate (1.19 g, 5.00 mmol, 62.25% yield, 95% purity) was obtained as a yellow solid.

LCMS (ESI) m/z: 227.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl)carbamate



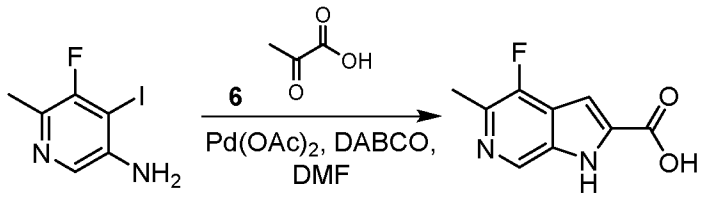
To a solution of tert-butyl N-(5-fluoro-6-methyl-3-pyridyl)carbamate (1.19 g, 5.26 mmol, 1 *eq*) and TMEDA (1.22 g, 10.52 mmol, 1.59 mL, 2 *eq*) in THF (10 mL) was added n-BuLi (2.5 M in n-hexane , 5.26 mL, 2.5 *eq*) dropwise at -78 °C under N_2. After stirring at -78 °C for 30 min, a solution of I_2 (2.00 g, 7.89 mmol, 1.59 mL, 1.5 *eq*) in THF (3 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 min. TLC (petroleum ether : ethyl acetate =3:1) indicated trace of starting material remained and new spots formed. The reaction mixture was quenched with saturated Na_2SO_3 (10 mL) at 25 °C, and then diluted with H_2O (5 mL) and extracted with EtOAc (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether). Compound tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl) carbamate (1.5 g, 3.83 mmol, 72.89% yield, 90% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 5-fluoro-4-iodo-6-methyl-pyridin-3-amine

4 **5**

To a solution of tert-butyl N-(5-fluoro-4-iodo-6-methyl-3-pyridyl) carbamate (1.5 g, 4.26 mmol, 1 *eq*) in DCM (15 mL) was added TFA (23.10 g, 202.59 mmol, 15 mL, 47.56 *eq*). The mixture was stirred at 25 °C for 12 hr. LC-MS indicated desired mass. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in sat. $NaHCO_3$ (5 mL), and then extracted with ethyl acetate (15 mL x 2). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-30% ethyl acetate in petroleum ether). Compound 5-fluoro-4-iodo-6-methyl-pyridin-3-amine (956 mg, 3.60 mmol, 84.60% yield, 95% purity) was obtained as a brown solid. ^{1}H NMR was recorded.

Synthesis of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

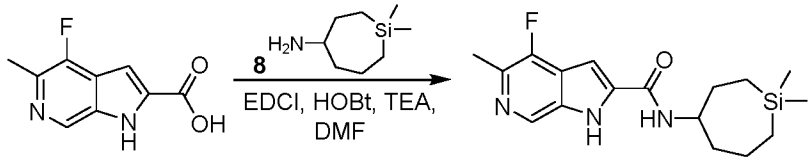


5 7

A mixture of 5-fluoro-4-iodo-6-methyl-pyridin-3-amine (956 mg, 3.79 mmol, 1 *eq*), 2-oxopropanoic acid (668.08 mg, 7.59 mmol, 534.46 uL, 2 *eq*) and DABCO (851.00 mg, 7.59 mmol, 834.31 uL, 2 *eq*) in DMF (10 mL) was degassed and purged with N_2 for 3 times, t$Pd(OAc)_2$ (170.32 mg, 758.65 umol, 0.2 *eq*) was then added. The mixture was stirred at 110 °C for 4 hr under N_2 atmosphere. LC-MS indicated desired mass. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to remove DMF. The residue was diluted with toluene (30 mL). The resulting suspension was sonicated for 30 min. The supernatant was poured off. The residue was diluted with H_2O (10 mL), and then adjusted to pH to 3-4 with aqueous HCl (1 N). The solid was collected by filtration. Compound 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2- carboxylic acid (695 mg, 3.58 mmol, 81.35% yield) was obtained as a brown solid.

LCMS (ESI) m/z: 195.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 13.54(br s, 1H), 12.51 (s, 1H), 8.57 (s, 1H), 7.09 (s, 1H), 2.48 (s, 3H).

Synthesis of N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide



7 MPL-351

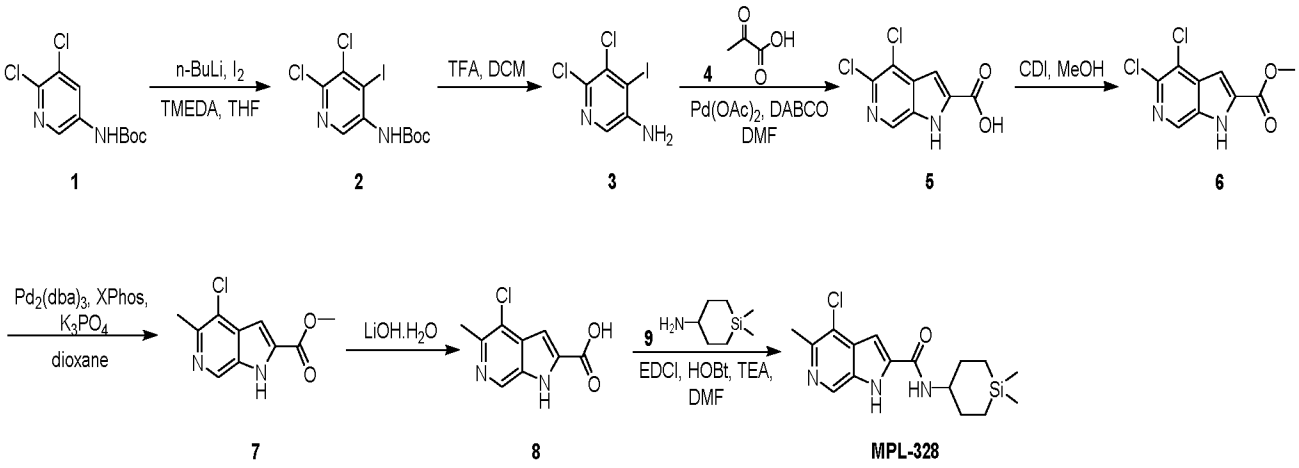
To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 257.52 umol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (59.88 mg, 309.02 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (148.10 mg, 772.55 umol, 3 *eq*) and HOBt (104.39 mg, 772.55 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (156.35 mg, 1.55 mmol, 215.06 uL, 6

eq). The mixture was stirred at 20 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.05% formic acid in water, B: CH3CN, gradient: 30%-60% B over 11 min). Compound N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (27.7 mg, 82.85 umol, 22.98% yield, 99.7% purity) was obtained as a white solid.

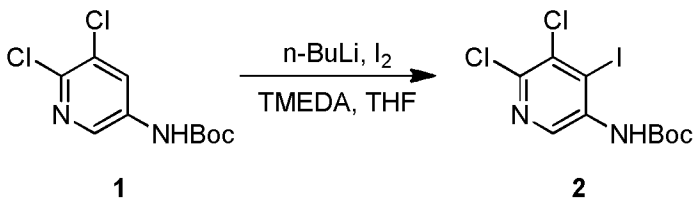
LCMS (ESI) m/z: 334.1 $[M+H]^+$; ^1H NMR (500MHz, METHANOL-d_4) δ = 8.52 (s, 1H), 7.19 (d, *J*=0.6 Hz, 1H), 4.01 - 3.90 (m, 1H), 2.53 (d, *J*=3.2 Hz, 3H), 2.10 - 1.88 (m, 3H), 1.85 - 1.71 (m, 1H), 1.63 - 1.51 (m, 2H), 0.89 - 0.63 (m, 4H), 0.06 (d, *J*=8.9 Hz, 6H).

Example 172. MPL-328

Scheme



Synthesis of tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate



To a solution of tert-butyl N-(5,6-dichloro-3-pyridyl)carbamate (11.5 g, 43.71 mmol, 1 *eq*) and TMEDA (10.16 g, 87.41 mmol, 13.19 mL, 2 *eq*) in THF (10 mL) was added n-BuLi (2.5 M in n-

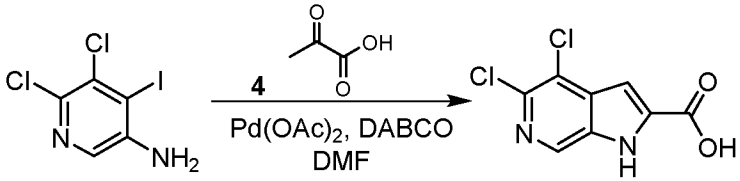
hexane, 43.71 mL, 2.5 *eq*) dropwise at -78 °C under N_2. After stirring at -78 °C for 30 min, a solution of I_2 (16.64 g, 65.56 mmol, 13.21 mL, 1.5 *eq*) in THF (10 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 min. TLC (Petroleum ether : Ethyl acetate=5:1) indicated compound 1 was consumed and many new spots formed. The reaction mixture was quenched with saturated Na_2SO_3 (60 mL) at 25 °C, and then extracted with EtOAc (60 mL x 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0% to 6% ethyl acetate in petroleum ether). Compound tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate (8.5 g, 18.57 mmol, 42.49% yield, 85% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 5,6-dichloro-4-iodo-pyridin-3-amine

2 **3**

To a solution of tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate (9.5 g, 24.42 mmol, 1 *eq*) in DCM (100 mL) was added TFA (162.56 g, 1.43 mol, 105.56 mL, 58.38 *eq*). The mixture was stirred at 30 °C for 12 hr. TLC (Petroleum ether : Ethyl acetate=5:1) indicated a new spot formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The resulting residue was dissolved in saturated $NaHCO_3$ (100 mL), and then extracted with ethyl acetate (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-22% ethyl acetate in petroleum ether). Compound 5,6-dichloro-4-iodo-pyridin-3-amine (6.4 g, 21.05 mmol, 86.18% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

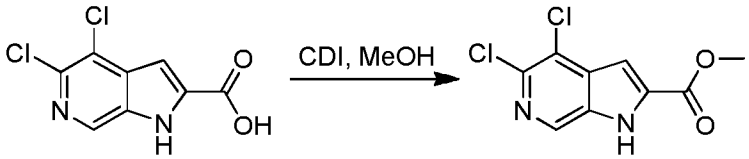


3 5

A mixture of 5,6-dichloro-4-iodo-pyridin-3-amine (3 g, 10.38 mmol, 1 *eq*), 2-oxopropanoic acid (1.83 g, 20.77 mmol, 1.46 mL, 2 *eq*), and DABCO (2.33 g, 20.77 mmol, 2.28 mL, 2 *eq*) in DMF (40 mL) was degassed and purged with N_2 for 3 times, and then $Pd(OAc)_2$ (466.27 mg, 2.08 mmol, 0.2 *eq*) was added into the solution. The mixture was stirred at 110 °C for 4 hr under N_2 atmosphere. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to remove DMF. The residue was diluted with toluene (60 mL). The suspension was sonicated for 30 minutes. The supernatant was removed. The residue was diluted with H_2O (50 mL), and pH was adjusted to 3-4 using aqueous HCl (1 N) and then filtered to collect the solid. Compound 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (2.7 g, 9.35 mmol, 90.03% yield, 80% purity) was obtained as a brown solid. The crude product was used for the next step without further purification.

LCMS (ESI) m/z 231.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



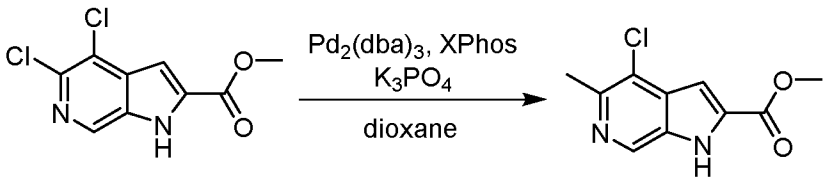
5 6

A mixture of 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (2.7 g, 11.69 mmol, 1 *eq*) and CDI (2.08 g, 12.86 mmol, 1.1 *eq*) in DMF (30 mL) was stirred at 30 °C for 1 hr. MeOH (23.75 g, 741.35 mmol, 30 mL, 63.44 *eq*) was then added. The mixture was stirred at 30 °C for 1 hr. LCMS indicated desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove MeOH and then poured into H_2O (300 mL). The precipitates were collected by filtration and dried under reduced pressure. Compound methyl 4,5-dichloro-1H-

pyrrolo[2,3-c] pyridine-2-carboxylate (480 mg, 1.86 mmol, 57.43% yield, 95% purity) was obtained as a brown solid, which was used for the next step without further purification.

LCMS (ESI) m/z: 245.0 $[M+H]^+$

Synthesis of methyl 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

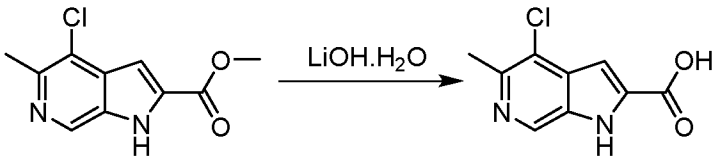


6 **7**

A mixture of methyl 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (500 mg, 2.04 mmol, 1 *eq*), methylboronic acid (610.66 mg, 10.20 mmol, 5 *eq*), K_3PO_4 (1.30 g, 6.12 mmol, 3 *eq*) and XPhos (194.53 mg, 408.06 umol, 0.2 *eq*) in dioxane (25 mL) was de-gassed under N_2 atmosphere. $Pd_2(dba)_3$ (373.67 mg, 408.06 umol, 0.2 *eq*) was then added. The suspension was degassed and purged with N_2 for 3 times. The mixture was stirred under N_2 at 120 °C for 12 hr. LC-MS showed desired mass was detected. EtOAc (60 mL) was added. The mixture was filtered to remove the insoluble materials. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, 0% to 34% ethyl acetate in petroleum ether). Compound methyl 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (62 mg, crude) was obtained as a yellow solid.

LCMS (ESI) m/z: 225.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

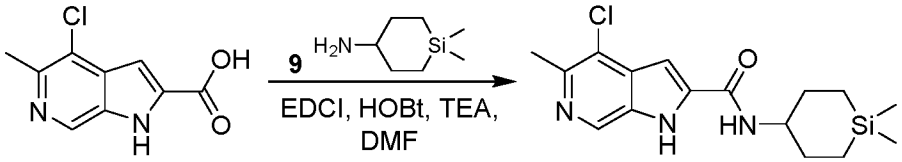


7 **8**

To a solution of methyl 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (110 mg, 489.67 umol, 1 *eq*) in THF (2 mL) was added a solution of $LiOH.H_2O$ (123.29 mg, 2.94 mmol, 6 *eq*) in H_2O (2 mL). The mixture was stirred at 60 °C for 2 hr. LC-MS showed desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove THF. The aqueous phase was adjusted to pH 3-4 with aqueous HCl (6 N), and then purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 30%-60% B over 11 min). Compound 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (15 mg, crude) was obtained as a white solid.

LCMS (ESI) m/z: 211.0 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.39 (s, 1H), 8.45 (s, 1H), 7.19 (s, 1H), 2.51 (s, 3H)

Synthesis of 4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



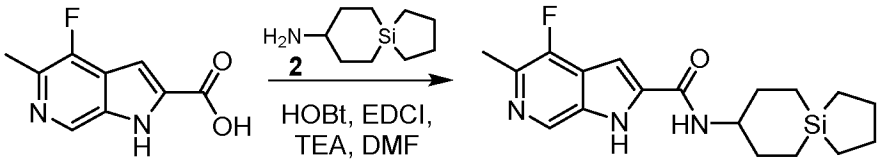
8 **MPL-328**

To a solution of 4-chloro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (15 mg, 71.22 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (15.36 mg, 85.46 umol, 1.2 *eq*, HCl salt) in DMF (2 mL) was added a solution of EDCI (40.96 mg, 213.66 umol, 3 *eq*) and HOBt (28.87 mg, 213.66 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (43.24 mg, 427.32 umol, 59.48 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired mass was detected. The reaction mixture was filtered. The filterate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 60%-80% B over 11 min) Compound 4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-methyl- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide (9.7 mg, 28.88 umol, 40.55% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 336.0 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 10.86 (br s, 1H), 8.64 (s, 1H), 6.88 (s, 1H), 6.50 (br s, 1H), 4.03 - 3.84 (m, 1H), 2.59 (s, 3H), 2.28 - 2.14 (m, 2H),1.72 - 1.56 (m, 2H), 0.86 - 0.80 (m, 2H), 0.77 - 0.64 (m, 2H), 0.09 (d, J=18.9 Hz, 6H).

Example 173. MPL-319

Synthesis of 4-fluoro-5-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



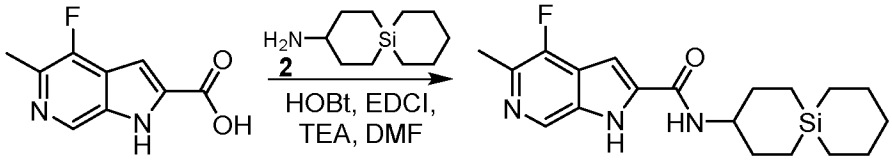
1 **MPL-319**

To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 257.52 umol, 1 *eq*), 5-silaspiro[4.5]decan-8-amine (79.50 mg, 386.28 umol, 1.5 *eq*, HCl salt) in DMF (1 mL) was added HOBt (104.39 mg, 772.55 umol, 3 *eq*), EDCI (148.10 mg, 772.55 umol, 3 *eq*) and TEA (156.35 mg, 1.55 mmol, 215.06 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired compound. The reaction mixture was diluted with water 5 mL and extracted with EtOAc 20 mL (10 mL x 2). The combined organic layer was washed with 5% LiCl (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150 x 30 mm x 5 um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 37%-65% B over 11 min). Compound 4-fluoro-5-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide (43.9 mg, 125.81 umol, 48.85% yield, 99.010% purity) was obtained as a white solid.

LCMS (ESI) m/z: 346.2 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d4) δ = 8.51 (d, J=0.8 Hz, 1H), 8.19 (br s, 1H), 7.18 (s, 1H), 3.83 (br t, J=11.3 Hz, 1H), 2.52 (d, J=3.1 Hz, 3H), 2.21 (br d, J=11.3 Hz, 2H), 1.72 - 1.58 (m, 6H), 0.88 - 0.82 (m, 4H), 0.68 (br t, J=6.8 Hz, 2H), 0.59 (br t, J=7.0 Hz, 2H).

Example 174. MPL-320

Synthesis of 4-fluoro-5-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



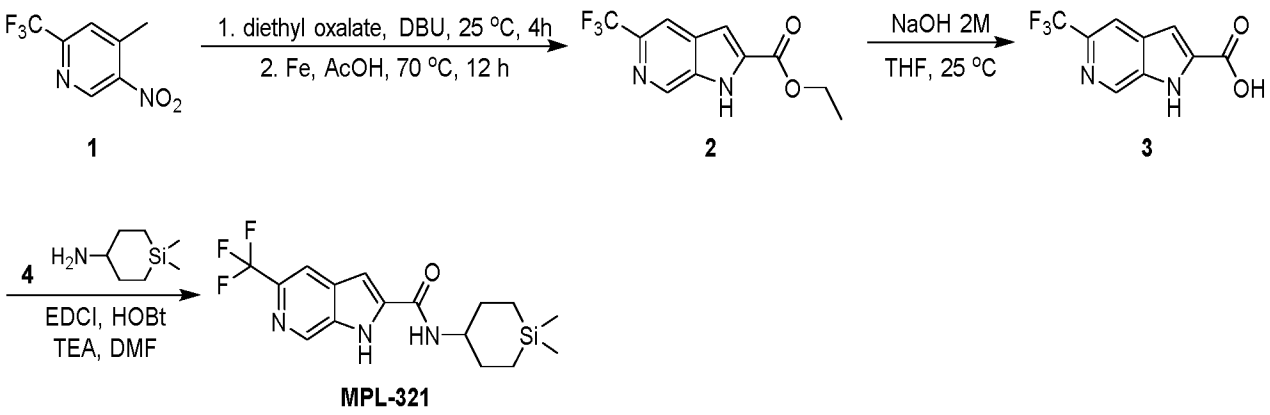
1 **MPL-320**

To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 257.52 umol, 1 *eq*), 6-silaspiro[5.5]undecan-3-amine (67.93 mg, 309.02 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added HOBt (104.39 mg, 772.55 umol, 3 *eq*), EDCI (148.10 mg, 772.55 umol, 3 *eq*) and TEA (156.35 mg, 1.55 mmol, 215.06 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired compound. The reaction mixture was diluted with CH_3OH (3 mL) and filtered. The filtrate was purified by prep-HPLC (column: YMC - Actus Triart C18 150 x 30 mm x 5 um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 52%-77% B over 11 min). Compound 4-fluoro-5-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo [2,3-c]pyridine- 2-carboxamide (55 mg, 152.99 umol, 59.41% yield, 100% purity) was obtained as a white solid.

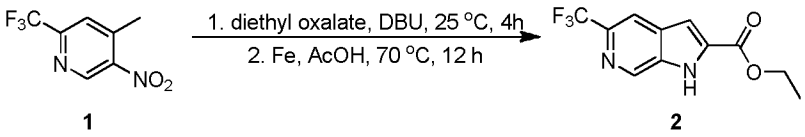
LCMS (ESI) m/z: 360.2 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d4) δ = 8.64 (s, 1H), 7.30 (s, 1H), 3.81 (br t, *J*=11.3 Hz, 1H), 2.60 (d, *J*=2.7 Hz, 3H), 2.15 (br d, *J*=9.8 Hz, 2H), 1.78 - 1.60 (m, 6H), 1.46 (br d, *J*=4.7 Hz, 2H), 0.98 (br d, *J*=14.9 Hz, 2H), 0.82 - 0.75 (m, 2H), 0.74 - 0.61 (m, 4H).

Example 175. MPL-321

Scheme

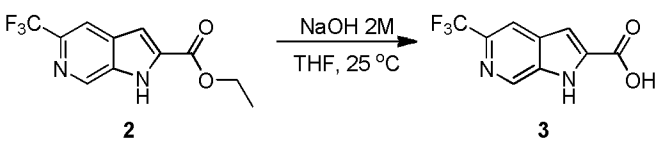


Synthesis of ethyl 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate



To a solution of 4-methyl-5-nitro-2-(trifluoromethyl)pyridine (900 mg, 4.37 mmol, 1 *eq*) in diethyl oxalate (2.99 g, 20.48 mmol, 2.80 mL, 4.69 *eq*) was added DBU (1.58 g, 10.35 mmol, 1.56 mL, 2.37 *eq*). After stirring at 25 °C for 4 hr, the mixture was concentrated under reduced pressure. The residue was redissolved in AcOH (18.90 g, 314.73 mmol, 18.00 mL, 72.08 *eq*). The mixture was heated to 60 °C and Fe (487.68 mg, 8.73 mmol, 2 *eq*) was added. The mixture was stirred at 70 °C for 12 hr. TLC (Petroleum ether : EtOAc = 3:1) showed one major spot. The mixture was poured into water (150 mL), filtered. The cake was re-dissolved in EtOAc (50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-30% Ethyl acetate in petroleum ether). Compound ethyl 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (800 mg, 2.94 mmol, 67.41% yield, 95% purity) was obtained as a light yellow solid. ^{1}H NMR was recorded.

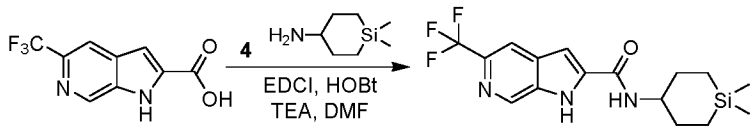
Synthesis of 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



To a solution of ethyl 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (800 mg, 3.10 mmol, 1 *eq*) in THF (10 mL) was added NaOH (1.60 g, 40.00 mmol, 12.91 *eq*) in H_2O (10 mL). The mixture was stirred at 25 °C for 60 hr. TLC (Petroleum ether : EtOAc = 5:1) showed the starting material was remained, one new spot formed. The mixture was stirred at 40 °C for additional 12 hr. TLC (Petroleum ether : EtOAc = 5:1) showed the starting material was consumed completely. The mixture was concentrated under reduced pressure to remove THF. Aq. HCl (3N) was added to adjust pH to 3. Solid was collected by filtration. The cake was washed by water (5 mL x 2) and petroleum ether (5 mL x 2) and dried by lyophilization. Compound 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine -2-carboxylic acid (700 mg, 2.89 mmol, 93.26% yield, 95% purity) was obtained as a light yellow solid.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 13.72 (br s, 1H), 12.79 (br s, 1H), 8.92 (s, 1H), 8.21 (s, 1H), 7.29 (d, *J*=1.2 Hz, 1H)

Synthesis of N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



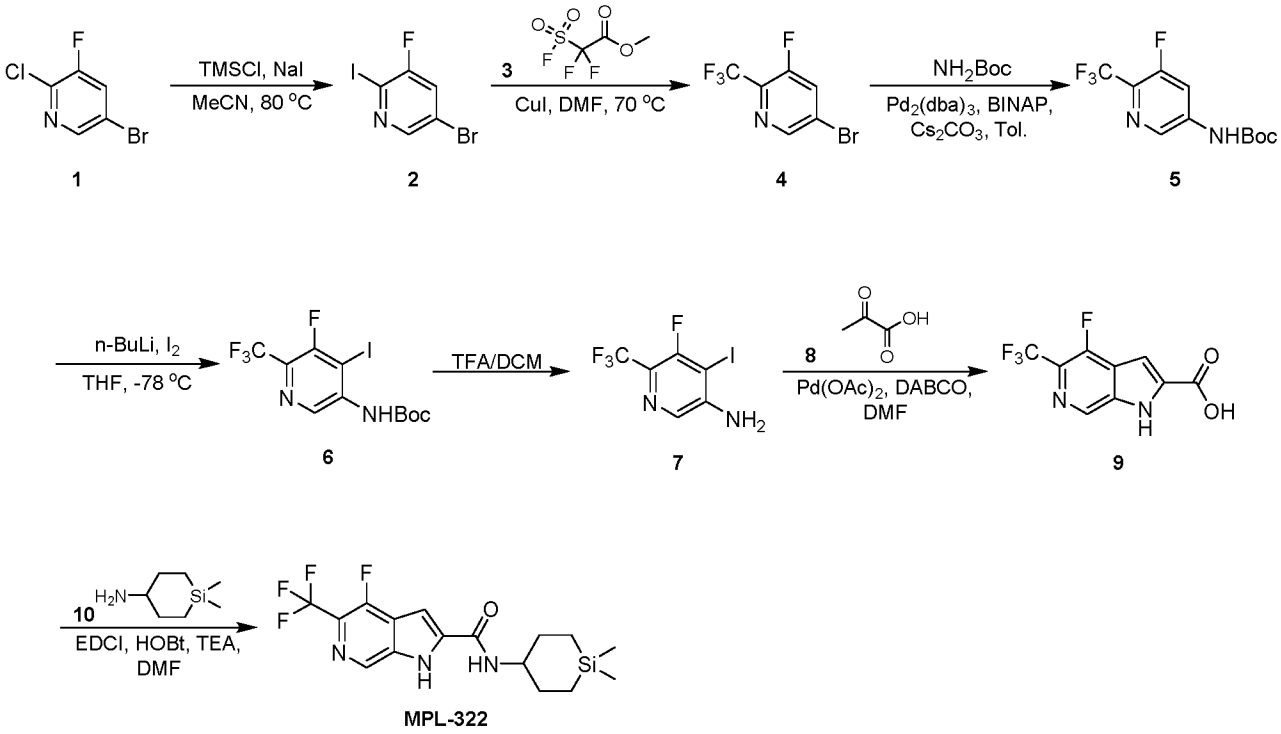
3 **MPL-321**

To a solution of 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (450 mg, 1.96 mmol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (421.79 mg, 2.35 mmol, 1.2 *eq*, HCl) in DMF (5 mL) was added a solution of EDCI (749.67 mg, 3.91 mmol, 2 *eq*) and HOBt (528.41 mg, 3.91 mmol, 2 *eq*) in DMF (5 mL), followed by TEA (791.42 mg, 7.82 mmol, 1.09 mL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was poured into aqueous $NaHCO_3$ solution (1 g in 100 mL water), and then filtered. The filter cake was washed with water (30 mL) under ultrasound for 1 h, and then filtered. The solid was then dried in vacuo for 2 h. Compound N-(1,1-dimethylsilinan-4-yl) -5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (512 mg, 1.44 mmol, 73.67% yield, 100% purity) was obtained as a white solid.

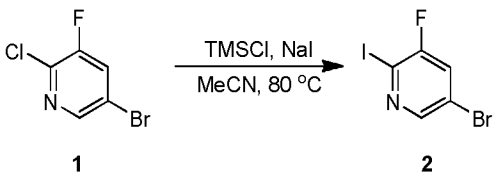
LCMS (ESI) m/z 356.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.42 (br s, 1H), 8.78 (s, 1H), 8.52 (d, *J*=8.1 Hz, 1H), 8.12 (d, *J*=0.8 Hz, 1H), 7.27 (s, 1H), 3.69 - 3.59 (m, 1H), 1.96 - 1.85 (m, 2H), 1.58 - 1.46 (m, 2H), 0.69 (br d, *J*=14.5 Hz, 2H), 0.53 (dt, *J*=4.8, 14.2 Hz, 2H), 0.05 - 10 (m, 6H).

Example 176. MPL-322

Scheme



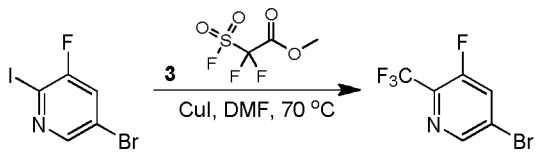
Synthesis of 5-bromo-3-fluoro-2-iodo-pyridine



To a solution of 5-bromo-2-chloro-3-fluoro-pyridine (5 g, 23.76 mmol, 1 *eq*) and NaI (10.68 g, 71.28 mmol, 3 *eq*) in CH_3CN (20 mL) was added TMSCl (2.58 g, 23.76 mmol, 3.02 mL, 1 *eq*). The mixture was stirred at 80 °C for 2 hr under N_2. LC-MS showed reactant and desired mass.

The reaction was stirred at 80 °C for additional 12 hr. TLC (Petroleum ether : EtOAc = 20:1) showed one major new spot with higher polarity. The reaction was quenched with saturated Na_2SO_3 (50 mL), and then concentrated under reduced pressure to remove CH_3CN. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-3% ethyl acetate in petroleum ether). All fractions containing product (checked by TLC, Petroleum ether : EtOAc = 20:1, Rf = 0.5) were collected and concentrated. Compound 5-bromo-3-fluoro-2-iodo-pyridine (2.5 g, crude) was obtained as a yellow oil.

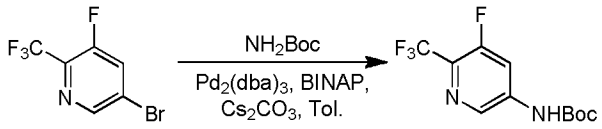
Synthesis of 5-bromo-3-fluoro-2-(trifluoromethyl)pyridine



2 4

To a solution of 5-bromo-3-fluoro-2-iodo-pyridine (4 g, 6.63 mmol, 1 *eq*) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (8.91 g, 46.38 mmol, 5.90 mL, 7 *eq*) in DMF (140 mL) was added CuI (8.83 g, 46.38 mmol, 7 *eq*). The mixture was stirred under N_2 at 60 °C for 12 hr. LCMS showed reactant was consumed completely and desired mass was detected. The mixture was filtered. The cake was washed with EtOAc (10 mL x 3). The combined filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc (200 mL), washed with LiCl (3%, 100 mL x 2) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-5% Ethyl acetate in petroleum ether). Fractions containing desired product (checked by TLC. Petroleum ether : EtOAc = 20:1) were combined and concentrated. Compound 5-bromo-3-fluoro-2-(trifluoromethyl)pyridine (900 mg, 1.84 mmol, 27.84% yield, 50% purity) was obtained as a yellow oil. ^1H NMR was recorded. It was used for the next step without further purification.

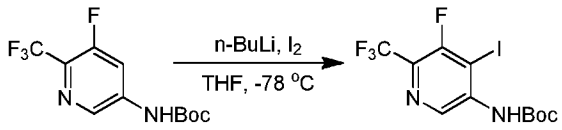
Synthesis of tert-butyl N-[5-fluoro-6-(trifluoromethyl)-3-pyridyl]carbamate



4 5

To a solution of 5-bromo-3-fluoro-2-(trifluoromethyl)pyridine (900 mg, 3.69 mmol, 1 *eq*), tert-butyl carbamate (1.30 g, 11.07 mmol, 3 *eq*) and Cs_2CO_3 (3.61 g, 11.07 mmol, 3 *eq*) in toluene (60 mL) was added $Pd_2(dba)_3$ (675.57 mg, 737.75 umol, 0.2 *eq*) and BINAP (689.07 mg, 1.11 mmol, 0.3 *eq*) under N_2. The mixture was degassed with N_2 for 15min, and stirred and refluxed at 110 °C for 12 hr. LCMS showed reactant was consumed completely and desired mass was detected. The mixture was filtered. The cake was washed with EtOAc (20 mL x 3). The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-8% ethyl acetate in petroleum ether). The fractions containing desired product (Checked by TLC, Petroleum ether : EtOAc = 5:1) were collected and concentrated. The resulting residue was further purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 52%-82% B over 11 min). Compound tert-butyl N-[5-fluoro-6-(trifluoromethyl)-3-pyridyl]carbamate (240 mg, 813.65 umol, 22.06% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of tert-butyl N-[5-fluoro-4-iodo-6-(trifluoromethyl)-3-pyridyl]carbamate



5 6

A solution of tert-butyl N-[5-fluoro-6-(trifluoromethyl)-3-pyridyl]carbamate (230 mg, 820.79 umol, 1 *eq*) in THF (10 mL) was purged with N_2. TMEDA (286.14 mg, 2.46 mmol, 371.61 uL, 3 *eq*) was then added. The mixture was cooled to -75 °C and n-BuLi (2.5 M in n-hexane, 820.79 uL, 2.5 *eq*) was added dropwise to maintain temperature below -70 °C. After addition, the mixture was stirred at -75 °C ~ -70 °C for 3 hr. Then a solution of I_2 (312.48 mg, 1.23 mmol, 248.00 uL, 1.5 *eq*) in THF (2 mL) was added at -70 °C dropwise to maintain temperature below -70 °C. The mixture was stirred at -75 °C ~ -70 °C for 2 hr. TLC (Petroleum ether : EtOAc = 5:1)

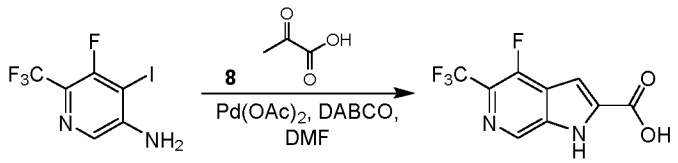
showed starting material was consumed completely and one major new sport formed. The reaction was quenched with saturated Na_2SO_3 (20 mL). The mixture was concentrated under reduced pressure to remove THF, and then extracted with EtOAc (10 mL x 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-20% Ethyl acetate in petroleum ether). Compound tert-butyl N-[5-fluoro-4-iodo-6-(trifluoromethyl)-3-pyridyl]carbamate (240 mg, 561.42 umol, 68.40% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of 5-fluoro-4-iodo-6-(trifluoromethyl)pyridin-3-amine

6 **7**

To a solution of tert-butyl N-[5-fluoro-4-iodo-6-(trifluoromethyl)-3-pyridyl]carbamate (240 mg, 590.97 umol, 1 *eq*) in DCM (2.5 mL) was added TFA (11.55 g, 101.30 mmol, 7.5 mL, 171.41 *eq*). The mixture was stirred at 25 °C for 3 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely and one new spot formed. Saturated $NaHCO_3$ was added to adjust pH to 8. The product was extracted with EtOAc (15 mL x 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. Compound 5-fluoro-4-iodo-6-(trifluoromethyl)pyridin-3-amine (190 mg, 589.87 umol, 99.81% yield, 95% purity) was obtained as a light yellow solid. ^{1}H NMR was recorded.

Synthesis of 4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



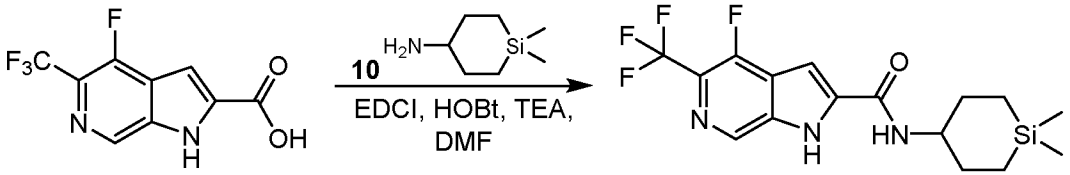
7 **9**

To a mixture of 5-fluoro-4-iodo-6-(trifluoromethyl)pyridin-3-amine (169 mg, 552.29 umol, 1 *eq*), 2-oxopropanoic acid (116.73 mg, 1.33 mmol, 93.38 uL, 2.4 *eq*) and DABCO (123.90 mg,

1.10 mmol, 121.47 uL, 2 *eq*) was added DMF (8 mL). Then $Pd(OAc)_2$ (62.00 mg, 276.14 umol, 0.5 *eq*) was added under N_2. The mixture was purged with N_2 for 15 min then stirred at 115 °C for 5 h. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to remove DMF. The residue was redissolved in MeOH and filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 6%-60%B over 11min). Compound 4-fluoro-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxylic acid (85 mg, 325.43 umol, 58.92% yield, 95% purity) was obtained as a white solid.

LCMS (ESI) m/z 248.9 $[M+H]^+$

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide



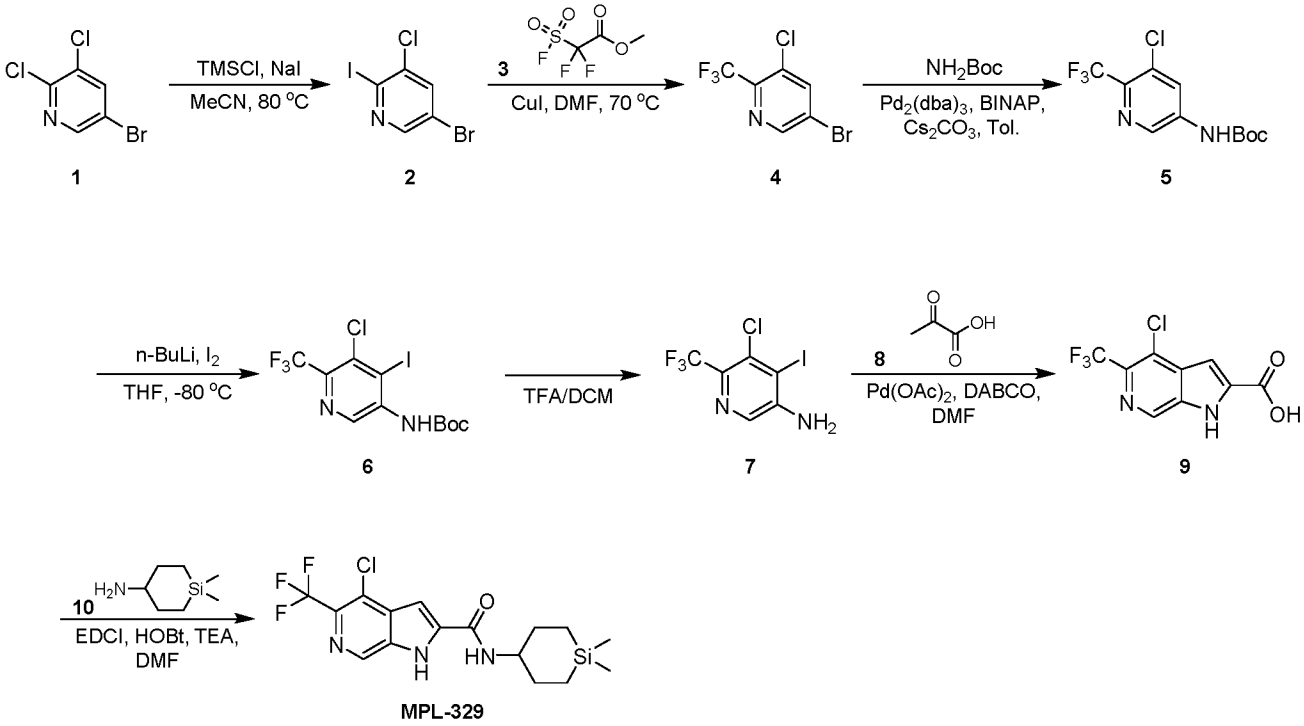
9 **MPL-322**

To a solution of 4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (65 mg, 261.96 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (61.22 mg, 340.54 umol, 1.3 *eq*, HCl salt) in DMF (0.7 mL) was added a solution of EDCI (100.43 mg, 523.91 umol, 2 *eq*) and HOBt (70.79 mg, 523.91 umol, 2 *eq*) in DMF (0.8 mL), followed by TEA (106.03 mg, 1.05 mmol, 145.84 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed reactant was consumed completely and one main peak with desired mass was detected. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient 66%-92% B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (70 mg, 187.46 umol, 71.56% yield, 100% purity) was obtained as a white solid.

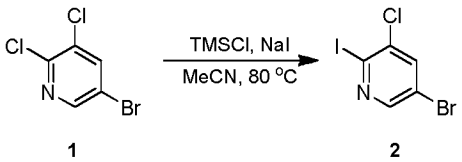
LCMS (ESI) m/z 374.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 13.45 - 12.02 (m, 1H), 8.61 (d, J=1.7 Hz, 1H), 8.52 (br d, J=8.1 Hz, 1H), 7.43 (s, 1H), 3.72 - 3.59 (m, 1H), 1.98 - 1.87 (m,2H), 1.58 - 1.47 (m, 2H), 0.69 (br d, J=14.5 Hz, 2H), 0.53 (dt, J=4.7, 14.1 Hz, 2H), 0.00 (s, 3H), -0.06 (s, 3H).

Example 177. MPL-329

Scheme



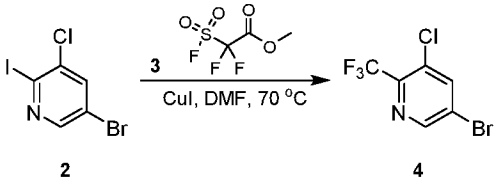
Synthesis of 5-bromo-3-chloro-2-iodo-pyridine



To a solution of 5-bromo-2,3-dichloro-pyridine (3 g, 13.22 mmol, 1 *eq*) and NaI (5.95 g, 39.67 mmol, 3 *eq*) in CH_3CN (30 mL) was added TMSCl (1.44 g, 13.22 mmol, 1.68 mL, 1 *eq*). The mixture was stirred at 80 °C under N_2 for 2 hr. LCMS showed one main peak with desired mass but compound 1 was also detected. The reaction was stirred at 80 °C for additional 12 hr. LCMS

showed desired mass and compound 1 was almost consumed completely. The reaction was quenched with saturated Na_2SO_3 (60 mL). The mixture was concentrated under reduced pressure to remove CH_3CN, and then was extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (40 mL x 2), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-2% Ethyl acetate in petroleum ether). The fractions containing product (checked by TLC. Petroleum ether : EtOAc = 20:1) were combined and concentrated. Compound 5-bromo-3-chloro-2-iodo-pyridine (3 g, 7.54 mmol, 57.02% yield, 80% purity) was obtained as a white solid. It was used for the next step without further purification.

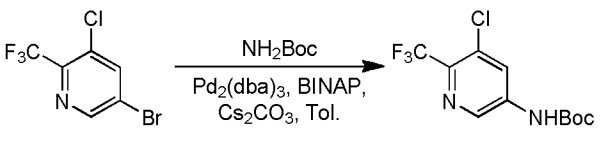
Synthesis of 5-bromo-3-chloro-2-(trifluoromethyl)pyridine



2 4

To a solution of 5-bromo-3-chloro-2-iodo-pyridine (3 g, 4.71 mmol, 1 *eq*) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (6.34 g, 32.98 mmol, 4.20 mL, 7 *eq*) in DMF (100 mL) was added CuI (6.28 g, 32.98 mmol, 7 *eq*). The mixture was stirred under N_2 at 60 °C for 12 hr. LC-MS showed reactant 2 was consumed completely and desired mass was detected. The mixture was concentrated under reduced pressure. The product was found in the residue as well as in the solution collected in flask (checked by TLC; petroleum ether : EtOAc = 20:1). The solution was poured to water (800 mL) and extracted with a mixture of petroleum ether and EtOAc (10:1, 300 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give compound 5-bromo-3-chloro-2-(trifluoromethyl)pyridine (890 mg, 2.73 mmol, 58.02% yield, 80% purity) as a colorless oil. ^1H NMR was recorded.

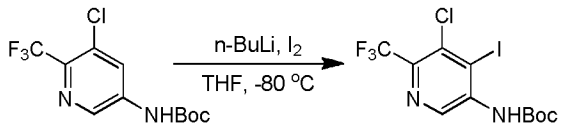
Synthesis of tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-pyridyl]carbamate



4 5

To a mixture of 5-bromo-3-chloro-2-(trifluoromethyl)pyridine (600 mg, 2.30 mmol, 1 *eq*), tert-butyl carbamate (809.64 mg, 6.91 mmol, 3 *eq*) and Cs_2CO_3 (2.25 g, 6.91 mmol, 3 *eq*) in toluene (45 mL) was added $Pd_2(dba)_3$ (421.93 mg, 460.76 umol, 0.2 *eq*) and BINAP (430.35 mg, 691.14 umol, 0.3 *eq*) under N_2. The mixture was degassed with N_2 for 15min and then stirred and refluxed at 110 °C for 12 hr. LC-MS showed reactant 4 was consumed completely and desired mass was detected. The mixture was filtered. The cake was washed with EtOAc (20 mL x 3). The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-12% Ethyl acetate in petroleum ether). The fractions containing product (checked by TLC, petroleum ether : EtOAc = 8:1) were collected and concentrated. Compound tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-pyridyl]carbamate (360 mg, 1.15 mmol, 50.04% yield, 95% purity) was obtained as a yellow solid. ^1H NMR was recorded.

Synthesis of tert-butyl N-[5-fluoro-4-iodo-6-(trifluoromethyl)-3-pyridyl]carbamate

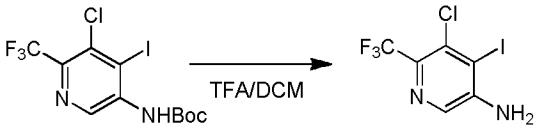


5 **6**

To a solution of tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-pyridyl]carbamate (480 mg, 1.62 mmol, 1 *eq*) in THF (20 mL) (dried by Na and distilled) was purged with N_2, and TMEDA (564.06 mg, 4.85 mmol, 732.55 uL, 3 *eq*) was then added. The mixture was cooled to -80 °C,n-BuLi (2.5 M in n-hexane, 1.75 mL, 2.7 *eq*) was the added dropwise to maintain temperature below -80 °C. After addition, the mixture was stirred at -80 °C ~ -90 °C for 3 hr. Then a solution of I_2 (698.10 mg, 2.75 mmol, 554.05 uL, 1.7 *eq*) in THF (5 mL) was added at -80 °C dropwise to maintain temperature below -80 °C. The mixture was stirred at -80 °C ~ -90 °C for 2 hr. TLC (petroleum ether : EtOAc = 5:1) showed one new sport formed. The reaction was quenched with saturated Na_2SO_3 (40 mL), concentrated under reduced pressure to remove THF. The aqueous solution was extracted with EtOAc (20 mL X 3). The combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-20% Ethyl acetate in petroleum ether). Compound tert-

butyl N-[5-chloro-4-iodo-6- (trifluoromethyl)-3-pyridyl]carbamate (400 mg, 899.26 umol, 55.58% yield, 95% purity) was obtained as a light yellow solid. ^{1}H NMR was recorded.

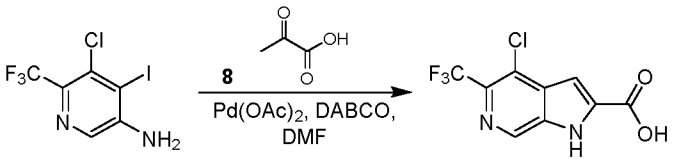
Synthesis of 5-chloro-4-iodo-6-(trifluoromethyl)pyridin-3-amine



6 **7**

To a solution of tert-butyl N-[5-chloro-4-iodo-6-(trifluoromethyl)-3-pyridyl]carbamate (400 mg, 946.59 umol, 1 *eq*) in DCM (5 mL) was added TFA (23.10 g, 202.60 mmol, 15 mL, 214.03 *eq*). The mixture was stirred at 25 °C for 3 hr. TLC (Petroleum ether : EtOAc = 3:1) showed starting material was consumed completely and one new spot formed. The mixture was concentrated under reduced pressure. The residue was poured into saturated $NaHCO_3$ (50 mL), and then extracted with EtOAc (20 mL). The organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Compound 5-chloro-4-iodo-6-(trifluoromethyl)pyridin- 3-amine (220 mg, 648.16 umol, 68.47% yield, 95% purity) was obtained as a light yellow solid. ^{1}H NMR was recorded.

Synthesis of 4-chloro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



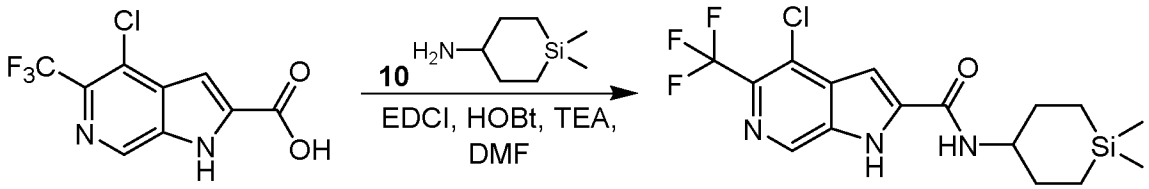
7 **9**

To a mixture of 5-chloro-4-iodo-6-(trifluoromethyl)pyridin-3-amine (200 mg, 620.24 umol, 1 *eq*), 2-oxopropanoic acid (81.93 mg, 930.37 umol, 65.54 uL, 1.5 *eq*) and DABCO (139.15 mg, 1.24 mmol, 136.42 uL, 2 *eq*) was added DMF (10 mL). Then $Pd(OAc)_2$ (55.70 mg, 248.10 umol, 0.4 *eq*) was added under N_2. The mixture was stirred at 115 °C for 4 hr. LCMS showed reactant 7 was consumed completely and one main peak with desired mass was detected. The mixture was concentrated under reduced pressure to remove DMF. The residue was redissolved in MeOH (4 mL), and then filtered to remove insoluble materials. The filtrate was purified by prep-HPLC

(column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 38%-60%B over11min). Compound 4-chloro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (28 mg, 105.82 umol, 17.06% yield) was obtained as a white solid.

LCMS (ESI) m/z 264.9 $[M+H]^+$

Synthesis of 4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide



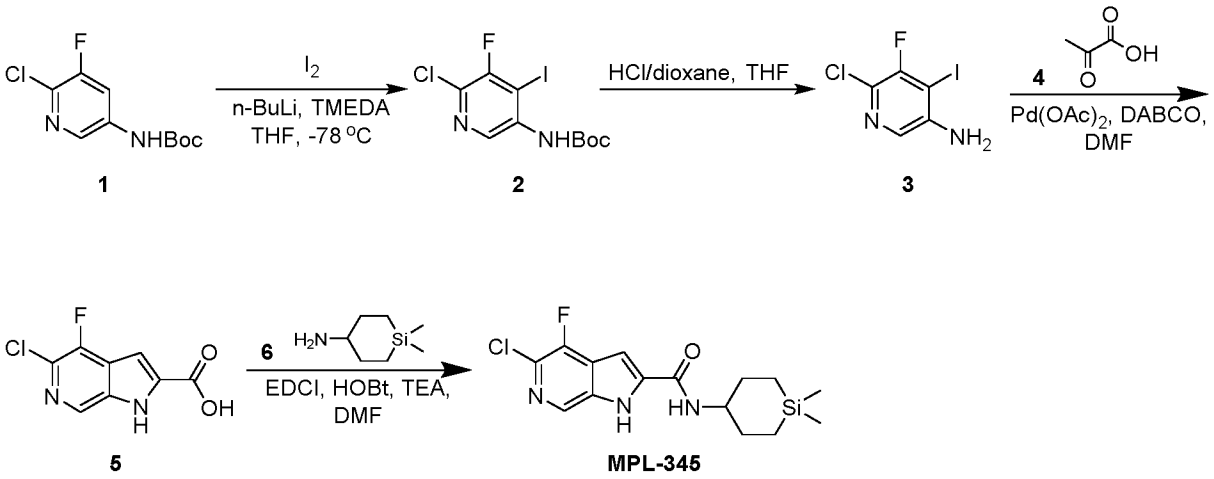
9 **MPL-329**

To a solution of 4-chloro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (28 mg, 105.82 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (26.63 mg, 148.15 umol, 1.4 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (40.57 mg, 211.65 umol, 2 *eq*) and HOBt (28.60 mg, 211.65 umol, 2 *eq*) in DMF (1 mL), followed by TEA (42.83 mg, 423.30 umol, 58.92 uL, 4 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed reactant remained. The mixture was stirred for additional 12 hr. LCMS showed reactant was consumed completely and one peak with desired mass was detected. The reaction mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 50%-70%B over 11min). Compound 4-chloro-N-(1,1-dimethylsilinan -4-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (27 mg, 69.25 umol, 65.44% yield, 100% purity) was obtained as a white solid.

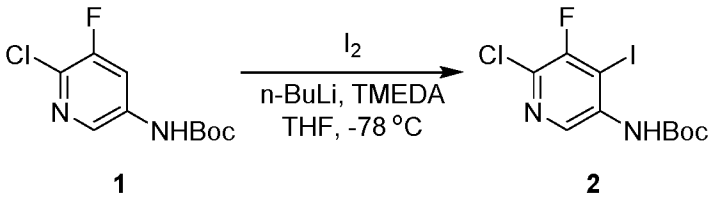
LCMS (ESI) m/z 390.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.79 (br s, 1H), 8.69 (s, 1H), 8.63 (br d, J=8.1 Hz, 1H), 8.66 - 8.59 (m, 1H), 7.45 (s, 1H), 3.65 (dt, J=8.0, 11.2 Hz, 1H),1.92 (br d, J=9.5 Hz, 2H), 1.60 - 1.44 (m, 2H), 0.69 (br d, J=14.3 Hz, 2H), 0.53 (dt, J=4.8, 14.2 Hz, 2H), 0.04 - -0.10 (m, 7H)

Example 178. MPL-345

Scheme

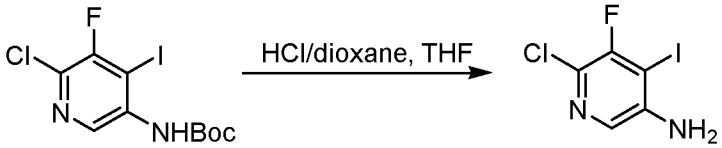


Synthesis of tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate



To a solution of tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (1 g, 4.05 mmol, 1 *eq*) and TMEDA (942.21 mg, 8.11 mmol, 1.22 mL, 2 *eq*) in THF (12 mL) was added n-BuLi (2.5 M in n-hexane, 4.05 mL, 2.5 *eq*) dropwise at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 30 mins. A solution of I_2 (1.54 g, 6.08 mmol, 1.22 mL, 1.5 *eq*) in THF (5 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 min. TLC (Petroleum ether : Ethyl acetate=3:1) indicated starting material was consumed completely and one new spot formed. The reaction mixture was quenched with saturated Na_2SO_3 (20 mL) at 25°C, and then diluted with H_2O (10 mL) and extracted with EtOAc(30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate (1.4 g, 3.57 mmol, 88.06% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

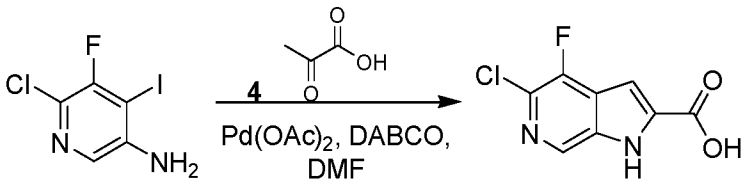
Synthesis of 6-chloro-5-fluoro-4-iodo-pyridin-3-amine



3 **4**

To a solution of tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate (1.4 g, 3.76 mmol, 1 *eq*) in THF (2 mL) was added HCl/dioxane (4 M, 5 mL, 5.32 *eq*). The mixture was stirred at 25 °C for 12 hr. TLC (Petroleum ether : Ethyl acetate=3:1) indicated starting material was consumed and one new spot formed. The resulting product was dissolved in Petroleum ether : Ethyl acetate = 5:1 (30 mL) and filtered to remove insoluble materials. The filtrate was concentrated in vacuo. The resulting residue was dissolved in saturated $NaHCO_3$ (5 mL), the and extracted with EtOAc (15 mL x 2). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound 6-chloro-5-fluoro-4-iodo-pyridin-3-amine (556 mg, 2.04 mmol, 54.31% yield) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid



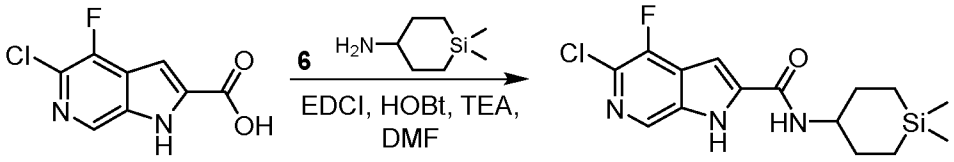
3 **5**

A mixture of 6-chloro-5-fluoro-4-iodo-pyridin-3-amine (456 mg, 1.67 mmol, 1 *eq*), 2-oxopropanoic acid (294.78 mg, 3.35 mmol, 235.83 uL, 2 *eq*), and DABCO (375.49 mg, 3.35 mmol, 368.13 uL, 2 *eq*) in DMF (5 mL) was degassed and purged with N_2 for 3 times, and then $Pd(OAc)_2$ (75.15 mg, 334.75 umol, 0.2 *eq*) was added. The mixture was stirred at 110 °C for 4 hr under N_2 atmosphere. LCMS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with toluene (15 mL). The suspension

was sonicated for 30 minutes, and the supernatant was poured off. The residue was diluted with H_2O (15 mL), and then adjusted to pH to 3-4 with aqueous HCl (1 N), and then filtered. The cake was collected and diluted with CH_3CN (6 mL). The suspension was sonicated for 10 minutes and filtered to collect solid. Compound 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (544 mg, crude) was obtained as a brown solid, which was used for the next step without further purification.

LCMS (ESI) m/z: 215.1 $[M+H]^{1+}$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.81 (s, 1H), 8.48 (s, 1H), 7.17 (s, 1H).

Synthesis of 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

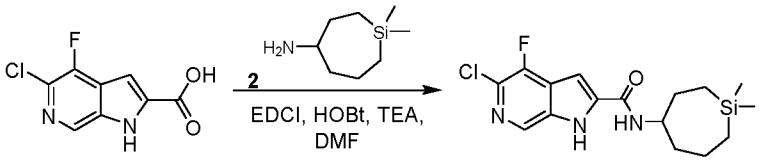


To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 466.02 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (100.53 mg, 559.23 umol, 1.2 *eq*, HCl salt) in DMF (2.5 mL) was added a solution of EDCI (268.01 mg, 1.40 mmol, 3 *eq*) and HOBt (188.91 mg, 1.40 mmol, 3 *eq*) in DMF (0.5 mL), followed by TEA (282.94 mg, 2.80 mmol, 389.19 uL, 6 *eq*) The mixture was stirred at 20 °C for 1 hr. LCMS showed desired mass. The reaction mixture was filtered to obtain the filter cake. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 55%-85% B over 11 min). Compound 5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide (66.6 mg, 195.96 umol, 42.05% yield, 100% purity) was obtained as a pale-orange solid.

LCMS (ESI) m/z: 340.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ= 12.61 (br s, 1 H) 8.59 (d, *J*=8.09 Hz, 1 H) 8.45 (s, 1 H) 7.37 (s, 1 H) 3.69 - 3.77 (m, 1 H) 1.96 - 2.04 (m, 2 H) 1.55 - 1.65 (m, 2 H) 0.78 (br d, *J*=14.34 Hz, 2 H) 0.62 (td, *J*=14.11, 4.58 Hz, 2 H) 0.00 - 0.12 (m, 6 H).

Example 179. MPL-346

Synthesis of 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide

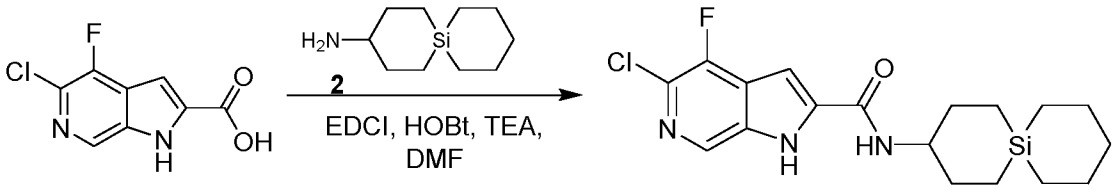


To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 233.01 umol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (54.19 mg, 279.61 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (134.01 mg, 699.04 umol, 3 *eq*) and HOBt (94.46 mg, 699.04 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (141.47 mg, 1.40 mmol, 194.59 uL, 6 *eq*) was added. The mixture was stirred at 20 °C for 1 hr. LC-MS indicated desired mass was detected. The reaction mixture was filtered to obtain filter residue, which was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient: 65%-90% B over 11 min). Compound 5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2- carboxamide (28.8 mg, 81.38 umol, 34.93% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 354.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 11.73 - 13.28 (m, 1 H) 8.60 - 8.64 (m, 1 H) 8.62 (br d, *J*=8.09 Hz, 1 H) 8.45 (s, 1 H) 7.39 (s, 1 H) 3.88 - 3.95 (m, 1 H) 1.79 - 1.96 (m, 3 H) 1.65 - 1.74 (m, 1 H) 1.45 - 1.56 (m, 2 H) 0.70 - 0.82 (m, 2 H) 0.58 - 0.66 (m, 2 H) 0.04 (d, *J*=10.83 Hz, 6 H).

Example 180. MPL-348

Synthesis of 5-chloro-4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



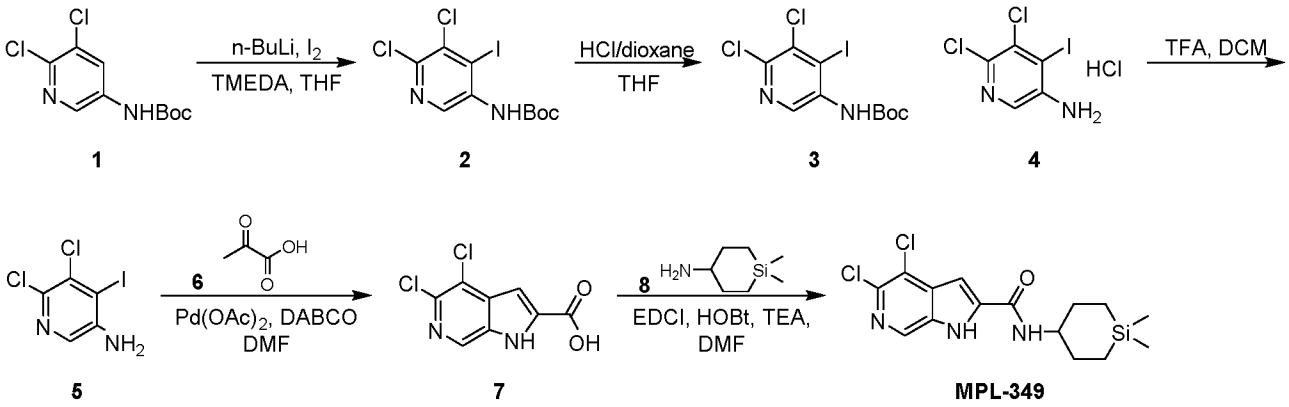
1 **MPL-348**

To a solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 233.01 umol, 1 eq) and 6-silaspiro[5.5]undecan-3-amine (61.47 mg, 279.61 umol, 1.2 eq, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (134.01 mg, 699.04 umol, 3 eq) and HOBt (94.46 mg, 699.04 umol, 3 eq) in DMF (0.5 mL), followed by TEA (141.47 mg, 1.40 mmol, 194.59 uL, 6 eq). The mixture was stirred at 20 °C for 1 hr. LC-MS showed compound 1 was consumed completely. The mixture was filtered and the filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient: 68%-97%B over 11 min.). Compound 5-chloro-4-fluoro-N-(6-silaspiro[5.5] undecan-3-yl) -1H-pyrrolo[2,3-c] pyridine-2-carboxamide (43.2 mg, 113.70 umol, 48.79% yield, 99.993% purity) was obtained as a white solid.

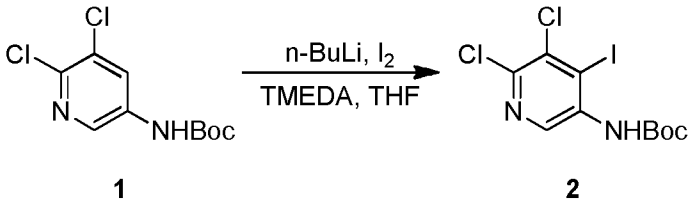
LCMS (ESI) m/z: 380.1 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-*d*6) δ = 0.54 - 0.65 (m, 4 H) 0.66 - 0.73 (m, 2 H) 0.90 (br d, *J*=14.65 Hz, 2 H) 1.38 (br s, 2 H) 1.53 - 1.70 (m, 6 H) 2.01 (br d, *J*=10.07 Hz, 2 H) 3.70 - 3.79 (m, 1 H) 7.35 (s, 1 H) 8.44 (s, 1 H) 8.59 (br d, *J*=7.93 Hz, 1 H) 12.42 - 12.87 (m, 1 H)

Example 181. MPL-349

Scheme

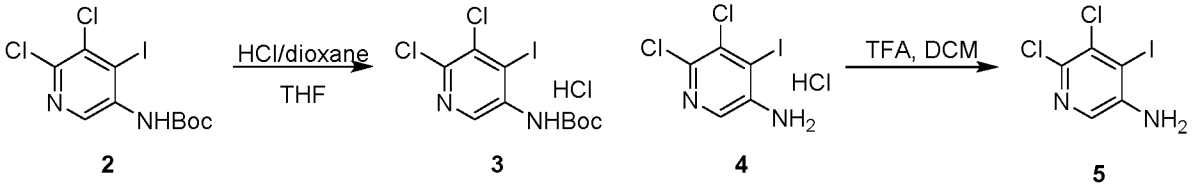


Synthesis of tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate



A mixture of tert-butyl N-(5,6-dichloro-3-pyridyl)carbamate (9 g, 34.20 mmol, 1 eq) in THF (100 mL) was degassed and purged with N_2 for 3 times, TMEDA (7.95 g, 68.41 mmol, 10.32 mL, 2 eq) and n-BuLi (2.5 M in hexane, 34.20 mL, 2.5 eq) was then added and the mixture was stirred at -60 °C for 30 min under N_2. A solution of I_2 (13.02 g, 51.31 mmol, 10.34 mL, 1.5 eq) in THF (20 mL) was added with stirring. The mixture was stirred at -60 °C for 30 min. TLC showed one major new spot with lower polarity. The reaction mixture was quenched with saturated Na_2SO_3 solution (100 mL) at 25 °C, and then diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layer was washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-5% Ethyl acetate in petroleum ether). Compound tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate (12.46 g, 25.61 mmol, 68.07% yield, 80% purity) was obtained as a yellow solid. ^1H NMR was recorded.

Synthesis of 5,6-dichloro-4-iodo-pyridin-3-amine

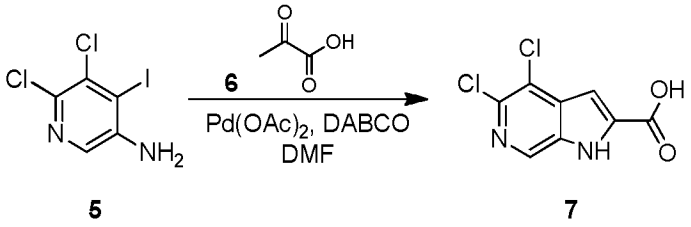


Step 1: To a solution of tert-butyl N-(5,6-dichloro-4-iodo-3-pyridyl)carbamate (12.46 g, 32.03 mmol, 1 eq) in THF (30 mL) was added HCl/dioxane (100 mL). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired compound formed. The mixture was filtered. The cake was collected. ^{1}H NMR analysis indicated that the filter cake (10.6g, yellow solid) was a mixture of compounds 3 and 4.

Step 2: A mixture of compound 3 and 4 (total 9.36g) was diluted with water (50 mL) and neutralized with saturated $NaHCO_3$ to pH 8, and then extracted with EtOAc (30 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL). TFA (8.24 g, 72.30 mmol, 5.35 mL, 8.62 eq) was added. The mixture was stirred at 25 °C for 1 hr. LCMS showed desired product. The mixture was adjusted to pH to 8 with saturated $NaHCO_3$, and then extracted with EtOAc (30 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Compound 5,6-dichloro-4-iodo-pyridin-3-amine (3.8 g, crude) was obtained as a yellow solid. The crude product was used for the next step without further purification.

LCMS (ESI) m/z 288.8 $[M+H]^+$; 1H NMR was recorded.

Synthesis of 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

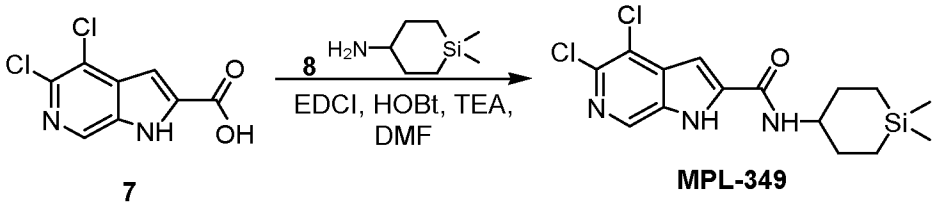


To a mixture of 5,6-dichloro-4-iodo-pyridin-3-amine (2 g, 6.92 mmol, 1 eq), 2-oxopropanoic acid (1.22 g, 13.85 mmol, 975.41 uL, 2 eq) and DABCO (1.55 g, 13.85 mmol, 1.52 mL, 2 eq) was added DMF (30 mL). The mixture was purged with N_2 and $Pd(OAc)_2$ (310.85 mg, 1.38

mmol, 0.2 eq) was added under N_2. The mixture was stirred at 110 °C for 4 hr. LCMS showed desired compound formed. The residue was filtered. The cake was washed with DMF (50 mL x 3). The combined organic layer was triturated with toluene (50 mL) at 25 °C for 20 min and filtered. The cake was then triturated with water (50 mL) at 25 °C for 20 min and filtered. The cake was then triturated with CH_3CN (50 mL) at 25 °C for 20 min and filtered. The solid was collected by filtration. Compound 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (1.1 g, 4.52 mmol, 59.40% yield, 95% purity) was obtained as a brown solid.

LCMS (ESI) m/z 230.7 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



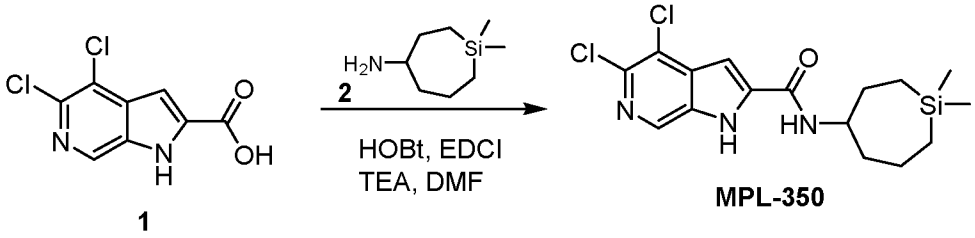
7 **MPL-349**

To a solution of 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 216.42 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (46.68 mg, 259.70 umol, 1.2 eq, HCl) in DMF (1 mL), a solution of HOBt (87.73 mg, 649.25 umol, 3 eq) and EDCI (124.46 mg, 649.25 umol, 3 eq) in DMF (1 mL) was added, followed by TEA (109.50 mg, 1.08 mmol, 150.61 uL, 5 eq). The reaction mixture was stirred at 25 °C for 2 hr. LCMS showed the starting material was consumed completely. The mixture was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 60%-90%B over 11min). Compound 4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (21.6 mg, 60.62 umol, 28.01% yield, 100% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 356.0 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.61 (br s, 1H), 8.66 (br d, J=8.4 Hz, 1H), 8.54 (s, 1H), 7.35 (s, 1H), 3.74 (br d, J=8.4 Hz, 1H), 2.01 (br d, J=9.5 Hz, 2H), 1.68 - 1.53 (m, 2H), 0.79 (br d, J=14.8 Hz, 2H), 0.62 (dt, J=4.8, 14.1 Hz, 2H), 0.10 (s, 3H), 0.04 (s, 3H).

Example 182. MPL-350

4,5-dichloro-N-(1,1-dimethylsilepan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

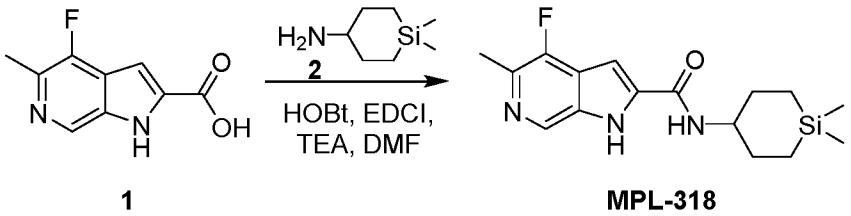


To a solution of 4,5-dichloro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 216.42 umol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (50.33 mg, 259.70 umol, 1.2 *eq*, HCl) in DMF (1 mL)， a solution of HOBt (87.73 mg, 649.25 umol, 3 *eq*) and EDCI (124.46 mg, 649.25 umol, 3 *eq*) in DMF (1 mL) was added with stirring, followed by TEA (109.50 mg, 1.08 mmol, 150.61 uL, 5 *eq*). The reaction mixture was stirred at 25 °C for 2 hr. LCMS showed desired compound formed. The mixture was purified by prep-HPLC (Gilson GX281, column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 65%-95% B over 11 min). Compound 4,5-dichloro-N-(1,1-dimethylsilepan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (19.7 mg, 53.19 umol, 24.58% yield, 100% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 370.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.54 (br s, 1H), 8.64 (d, *J*=8.1 Hz, 1H), 8.49 (s, 1H), 7.32 (s, 1H), 4.04 - 3.74 (m, 1H), 1.91 - 1.73 (m, 3H), 1.71 - 1.58 (m, 1H), 1.52 - 1.37 (m, 2H), 0.78 - 0.63 (m, 2H), 0.62 - 0.52 (m, 2H), -0.01 (d, *J*=11.7 Hz, 6H).

Example 183. MPL-318

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

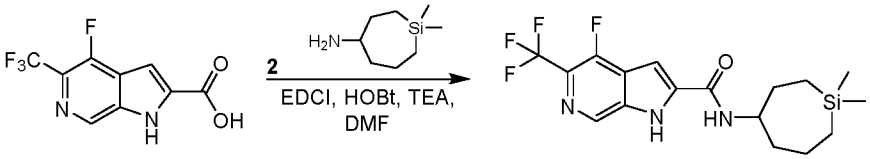


To a solution of 4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 206.01 umol, 1 *eq*), 1,1-dimethylsilinan-4-amine (44.44 mg, 247.22 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added HOBt (41.76 mg, 309.02 umol, 1.5 *eq*), EDCI (59.24 mg, 309.02 umol, 1.5 *eq*) and TEA (62.54 mg, 618.04 umol, 86.02 uL, 3 *eq*). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was diluted with CH_3OH (2 mL) and filtered. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150x30mmx5um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 35%-65% B over 11 min). Compound N-(1, 1-dimethylsilinan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2- carboxamide (24.2 mg, 74.87 umol, 36.34% yield, 98.8% purity) was obtained as a white solid.

LCMS (ESI) m/z 320.3 $[M+H]^+$; ^1H NMR (400MHz, METHANOL-d4) δ = 8.52 (s, 1H), 7.19 (s, 1H), 3.79 (br t, *J*=11.5 Hz, 1H), 2.53 (d, *J*=3.1 Hz, 3H), 2.14 (br d, *J*=9.8 Hz, 2H), 1.75 - 1.62 (m, 2H), 0.89 - 0.81 (m, 2H), 0.77 - 0.65 (m, 2H), 0.13 (s, 3H), 0.05 (s, 3H).

Example 184. MPL-366

Synthesis of N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide



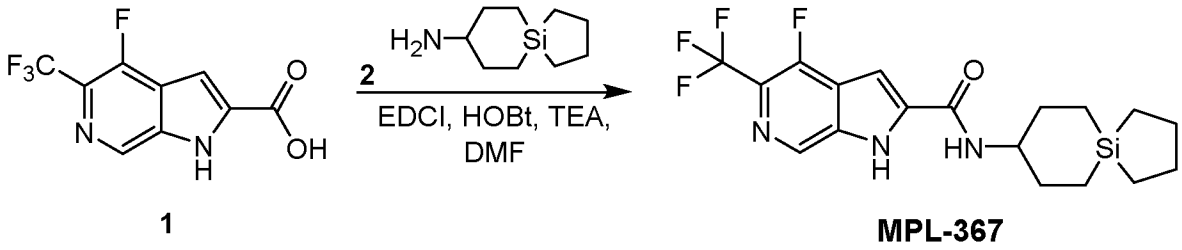
To a solution of 4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 241.80 umol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (60.92 mg, 314.35 umol, 1.3 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (92.71 mg, 483.61 umol, 2 *eq*) and HOBt (65.35 mg, 483.61 umol, 2 *eq*) in DMF (1 mL), followed by TEA (97.87 mg, 967.22 umol, 134.62 uL, 4 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed desired mass. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water; B: CH_3CN; gradient: 65%-90%B over 11 min). Compound N-(1,1-dimethylsilepan-4-yl)-

4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (8.8 mg, 22.71 umol, 9.39% yield, 100% purity) was obtained as a light yellow soild.

LCMS (ESI) m/z 388.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 13.33 - 12.20 (m, 1H), 8.65 (d, *J*=2.0 Hz, 1H), 8.62 (br d, *J*=8.1 Hz, 1H), 7.57 - 7.33 (m, 1H), 3.96 - 3.79 (m, 1H), 1.95 - 1.73 (m, 3H), 1.71 - 1.59 (m, 1H), 1.55 - 1.37 (m, 2H), 0.78 - 0.53 (m, 4H), -0.01 (d, *J*=11.0 Hz, 6H).

Example 185. MPL-367

Synthesis of 4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide

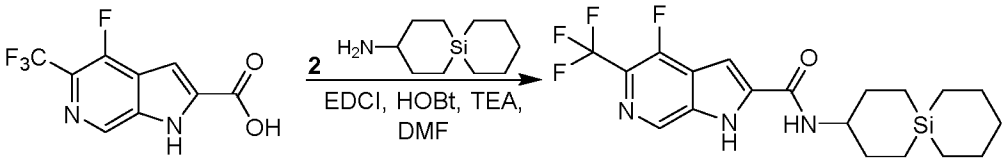


To a solution of 4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 403.01 umol, 1 *eq*) and 5-silaspiro[4.5]decan-8-amine (99.53 mg, 483.61 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (154.51 mg, 806.02 umol, 2 *eq*) and HOBt (108.91 mg, 806.02 umol, 2 *eq*) in DMF (1 mL), followed by TEA (163.12 mg, 1.61 mmol, 224.38 uL, 4 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed desired mass. The reaction mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH3CN; gradient: 67%-95%B over 11 min). Compound 4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (102 mg, 255.04 umol, 63.28% yield, 99.88% purity) was obtained as a brown solid.

LCMS (ESI) m/z 400.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.90 (br s, 1H), 8.71 (d, *J*=2.1 Hz, 1H), 8.67 (d, *J*=8.2 Hz, 1H), 7.54 (s, 1H), 3.86 - 3.73 (m, 1H), 2.17 - 2.03 (m, 2H), 1.69 - 1.50 (m, 6H), 0.86 - 0.69 (m, 4H), 0.66 - 0.44 (m, 4H).

Example 186. MPL-368

Synthesis of 4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-5-(trifluoromethyl)- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide



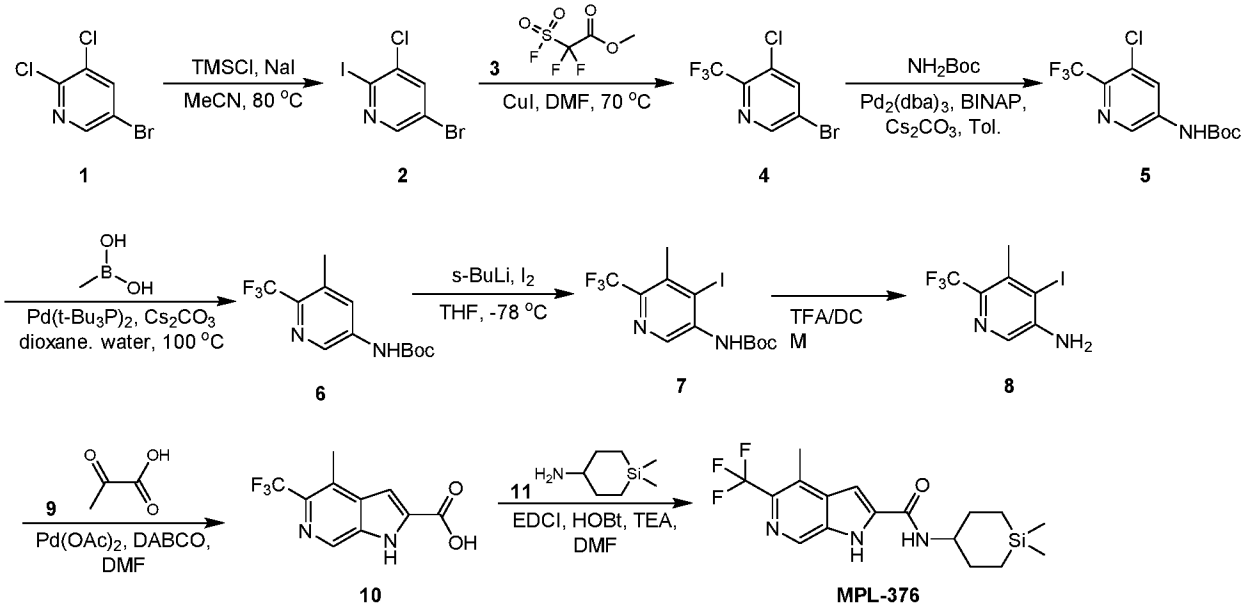
1 MPL-368

To a solution of 4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (60 mg, 241.80 umol, 1 *eq*) and 6-silaspiro[5.5]undecan-3-amine (63.79 mg, 290.17 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (92.71 mg, 483.61 umol, 2 *eq*) and HOBt (65.35 mg, 483.61 umol, 2 *eq*) in DMF (1 mL), followed by TEA (97.87 mg, 967.22 umol, 134.62 uL, 4 *eq*). The mixture was stirred at 30 °C for 2 hr. LCMS showed desired mass. The mixture was filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 70%-100%B over 11min). Compound 4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-5-(trifluoromethyl) -1H-pyrrolo[2,3-c]pyridine-2-carboxamide (16.8 mg, 40.63 umol, 16.80% yield, 100% purity) was obtained as a light yellow solid.

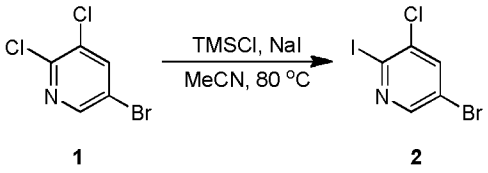
LCMS (ESI) m/z 414.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.91 (br s, 1H), 8.71 (d, *J*=2.0 Hz, 1H), 8.66 (br d, *J*=8.1 Hz, 1H), 7.65 - 7.34 (m, 1H), 3.76 (br d, *J*=8.2 Hz, 1H), 2.09 - 1.95 (m, 2H), 1.77 - 1.53 (m, 6H), 1.39 (br s, 2H), 0.92 (br d, *J*=14.6 Hz, 2H), 0.76 - 0.53 (m, 6H).

Example 187. MPL-376

Scheme

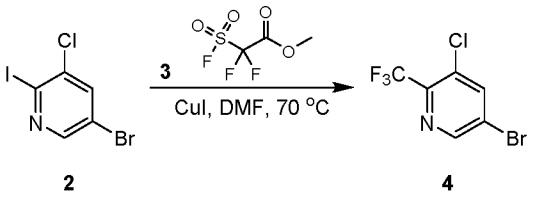


Synthesis of 5-bromo-3-chloro-2-iodo-pyridine



To a solution of 5-bromo-2,3-dichloro-pyridine (15 g, 66.11 mmol, 1 *eq*) and NaI (29.73 g, 198.34 mmol, 3 *eq*) in MeCN (100 mL) was added TMSCl (7.18 g, 66.11 mmol, 8.39 mL, 1 *eq*). The mixture was stirred at 80 °C under N_2 for 12 hr. TLC (petroleum ether : EtOAc = 20:1) showed starting material was consumed completely, and one major new spot formed. The reaction mixture was poured into saturated Na_2SO_3 (500 mL). The mixture was concentrated under reduced pressure to remove MeCN, and then extracted with EtOAc (200 mL x 2). The combined organic layer was washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-2% ethyl acetate in petroleum ether). Compound 5-bromo-3-chloro-2-iodo-pyridine (13 g, 24.50 mmol, 37.06% yield, 60% purity) was obtained as a white solid. ^{1}H NMR was recorded

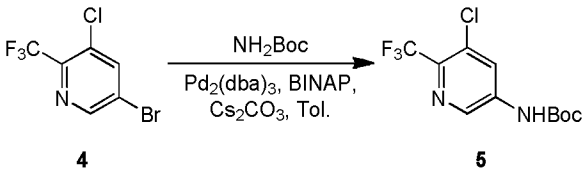
Synthesis of 5-bromo-3-chloro-2-(trifluoromethyl)pyridine



2 4

To a solution of 5-bromo-3-chloro-2-iodo-pyridine (10 g, 15.71 mmol, 1 *eq*) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (21.12 g, 109.95 mmol, 13.99 mL, 7 *eq*) in DMF (150 mL) was added CuI (20.94 g, 109.95 mmol, 7 *eq*). The mixture was stirred under N_2 at 60 °C for 12 hr. TLC (Petroleum ether : EtOAc = 20:1) showed one major spot. The mixture was poured into water (1.5 L) and extracted with n-pentane (500 mL). The organic layer was washed with aqueous LiCl (3%, 100 mL x 2) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-10% ethyl acetate in petroleum ether). Compound 5-bromo-3-chloro-2-(trifluoromethyl)pyridine (9 g, 13.82 mmol, 88.01% yield, 40% purity) was obtained as a colorless oil. ^{1}H NMR was recorded. The crude product was used for the next step without further purification.

Synthesis of tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-pyridyl]carbamate

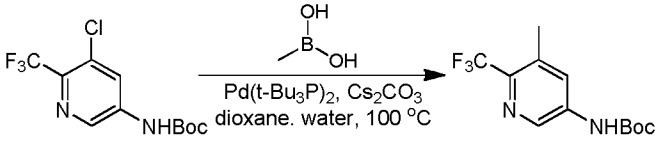


4 5

To a mixture of 5-bromo-3-chloro-2-(trifluoromethyl)pyridine (7 g, 26.88 mmol, 1 *eq*), tert-butyl carbamate (9.45 g, 80.63 mmol, 3 *eq*) and Cs_2CO_3 (26.27 g, 80.63 mmol, 3 *eq*) in toluene (150 mL) was added $Pd_2(dba)_3$ (1.23 g, 1.34 mmol, 0.05 *eq*) and BINAP (1.67 g, 2.69 mmol, 0.1 *eq*) under N_2. The mixture was degassed with N_2 for 15min and then stirred and refluxed at 110 °C for 12 hr. TLC (petroleum ether : EtOAc = 8:1) showed one major spot. The mixture was filtered. The cake was washed by EtOAc (20 mL x 3). The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-15% ethyl acetate in petroleum ether). Compound tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-

pyridyl]carbamate (3 g, 8.09 mmol, 30.10% yield, 80% purity) was obtained as a yellow solid. ^{1}H NMR was recorded.

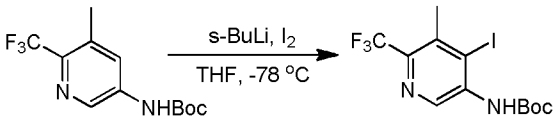
Synthesis of tert-butyl N-[5-methyl-6-(trifluoromethyl)-3-pyridyl]carbamate



5 **6**

To a mixture of $MeB(OH)_2$ (6.05 g, 101.12 mmol, 10 *eq*), Cs_2CO_3 (6.44 g, 19.76 mmol, 1.95 *eq*) and $Pd(t\text{-}Bu_3P)_2$ (1.03 g, 2.02 mmol, 0.2 *eq*) was added a solution of tert-butyl N-[5-chloro-6-(trifluoromethyl)-3-pyridyl]carbamate (3 g, 10.11 mmol, 1 *eq*) in dioxane (100 mL) and H_2O (1 mL). The mixture was purged with N_2 and stirred at 100 °C for 12 hr under N_2. LCMS showed desired mass. The mixture was filtered. The cake was washed with EtOAc (20 mL x 2). The combined filtrate was concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-20% ethyl acetate in petroleum ether). The fractions containing desired product (checked by TLC; petroleum ether : EtOAc = 3:1) were collected and concentrated. The resulting residue was further purified by prep-HPLC (column: Xtimate C18 150*40mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient: 52%-872% B over 8 min). Compound tert-butyl N-[5-methyl-6-(trifluoromethyl)-3-pyridyl]carbamate (1.3 g, 4.66 mmol, 46.07% yield, 99% purity) was obtained as a white solid. ^{1}H NMR was recorded.

Synthesis of tert-butyl N-[4-iodo-5-methyl-6-(trifluoromethyl)-3-pyridyl]carbamate

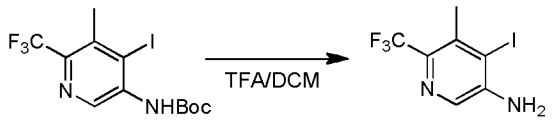


6 **7**

To a solution of tert-butyl N-[5-methyl-6-(trifluoromethyl)-3-pyridyl]carbamate (1.1 g, 3.98 mmol, 1 *eq*) in THF (40) (dried by Na and distilled freshly) was added TMEDA (1.39 g, 11.95 mmol, 1.80 mL, 3 *eq*). The mixture was cooled to -78 °C under N_2. Then s-BuLi (0.9 M in n-

hexane, 13.27 mL, 3 *eq*) was added dropwise, the mixture was stirred at -78 °C for 1 hr. A solution of I_2 (3.03 g, 11.95 mmol, 2.41 mL, 3 *eq*) in THF (10 mL) (dried with Na and distilled freshly) was added to the mixture dropwise, the mixture was stirred for 1 hr. TLC (Petroleum ether : EtOAc = 5:1) showed starting material was remained, one spot with lower polarity formed. The reaction was quenched with Na_2SO_3 (Sat. 50 mL), the mixture was diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (30 mL). The combined organic layer was dried by Na_2SO_4, and then filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-7% Ethyl acetate in petroleum ether). Compound tert-butyl N-[4-iodo-5-methyl -6-(trifluoromethyl)-3-pyridyl]carbamate (450 mg, 1.06 mmol, 26.70% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

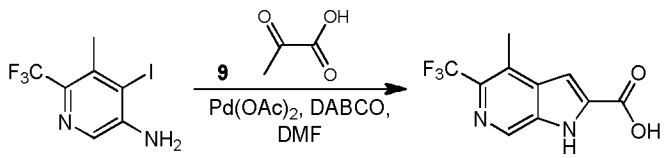
Synthesis of 4-iodo-5-methyl-6-(trifluoromethyl)pyridin-3-amine



7 **8**

To a solution of tert-butyl N-[4-iodo-5-methyl-6-(trifluoromethyl)-3-pyridyl]carbamate (480 mg, 1.19 mmol, 1 *eq*) in DCM (5 mL) was added TFA (3.02 g, 26.46 mmol, 1.96 mL, 22.17 *eq*). The mixture was stirred at 20 °C for 3 hr. TLC (petroleum ether : EtOAc = 3 :1) showed starting material remained. Additional TFA (1 mL) was added. The mixture was stirred at 20 °C for 4 h. TLC (petroleum ether : EtOAc = 3 :1) showed starting material was consumed completely. The mixture was concentrated under reduced pressure. The resulting residue was diluted with saturated $NaHCO_3$ (20 mL), and then extracted with EtOAc (10 mL x 2). The combined organic layer was dried by Na_2SO_4, and then filtered and concentrated under reduced pressure. Compound 4-iodo-5-methyl-6-(trifluoromethyl)pyridin-3-amine (380 mg, 1.13 mmol, 94.87% yield, 90% purity) was obtained as a brown solid. ^{1}H NMR was recorded.

Synthesis of 4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

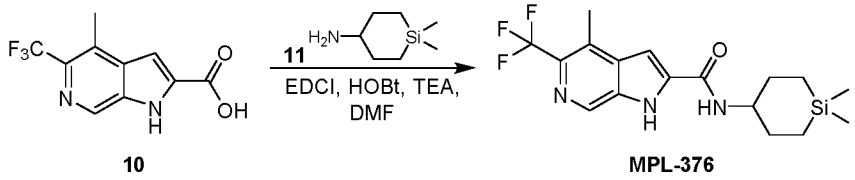


8 10

To a mixture of 4-iodo-5-methyl-6-(trifluoromethyl)pyridin-3-amine (350 mg, 1.16 mmol, 1 *eq*), 2-oxopropanoic acid (204.09 mg, 2.32 mmol, 163.27 uL, 2 *eq*) and DABCO (324.97 mg, 2.90 mmol, 318.60 uL, 2.5 *eq*) was added DMF (20 mL), followed by $Pd(OAc)_2$ (52.03 mg, 231.76 umol, 0.2 *eq*) under N_2. The mixture was stirred at 115 °C for 5 hr under N_2. LCMS showed one major peak with desired mass. The mixture was concentrated under reduced pressure. The resulting residue was diluted with MeOH (5 mL) and then filtered to remove insoluble matter. The fitrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 25%-55% B over 11 min). Compound 4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxylic acid (190 mg, 739.24 umol, 63.79% yield, 95% purity) was obtained as a brown solid.

LCMS (ESI) m/z 245.0 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.67 (br s, 1H), 8.71 (s, 1H), 7.42 (d, *J*=1.1 Hz, 1H), 2.66 (d, *J*=1.8 Hz, 3H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



10 MPL-376

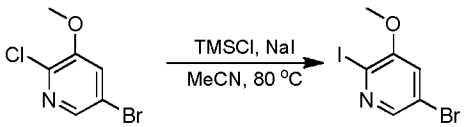
To a solution of 4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (70 mg, 286.69 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (61.84 mg, 344.02 umol, 1.2 *eq*, HCl salt) in DMF (2 mL) was added a solution of EDCI (109.92 mg, 573.37 umol, 2 *eq*) and HOBt (77.48 mg, 573.37 umol, 2 *eq*) in DMF (2 mL), followed by TEA (116.04 mg, 1.15 mmol, 159.61 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LCMS showed one main peak with desired mass. The mixture was filtered to remove insoluble matter. The filtrate was purified by

prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 63%-93%B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (63.5 mg, 171.87 umol, 59.95% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z 370.2 $[M+H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ = 12.35 (br s, 1H), 8.57 (s, 1H), 8.47 (d, *J*=8.1 Hz, 1H), 7.37 (s, 1H), 3.69 - 3.60 (m, 1H), 3.69 - 3.60 (m, 1H), 2.54 (d, *J*=1.7 Hz, 3H), 1.96 - 1.85 (m, 2H), 1.59 - 1.44 (m, 2H), 0.69 (br d, *J*=14.5 Hz, 2H), 0.53 (dt, *J*=4.7, 14.2 Hz, 2H), 0.03 - 0.11 (m, 6H).

Example 188. MPL-379

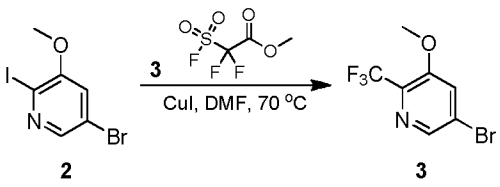
Synthesis of 5-bromo-2-iodo-3-methoxy-pyridine



1 2

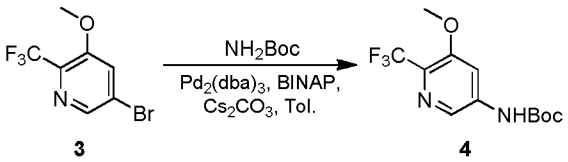
To a solution of 5-bromo-2-chloro-3-methoxy-pyridine (500 mg, 2.25 mmol, 1 *eq*) in MeCN (10 mL) was added NaI (1.01 g, 6.74 mmol, 3 *eq*), followed by TMSCl (244.17 mg, 2.25 mmol, 285.25 uL, 1 *eq*). The mixture was stirred at 80 °C for 12 hr. LCMS showed starting material was consumed completely, and desired mass was detected. The reaction mixture was poured into saturated Na_2SO_3 (10 mL). The mixture was concentrated under reduced pressure to remove MeCN, and then extracted by EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-5% ethyl acetate in petroleum ether). The fractions containing desired product (checked by TLC; petroleum ether : EtOAc = 20 : 1) were collected and concentrated. Compound 5-bromo-2-iodo-3- methoxy-pyridine (600 mg, 1.53 mmol, 68.03% yield, 80% purity) was obtained as a white solid. ^1H NMR was recorded.

Step 2. Synthesis of 5-bromo-3-methoxy-2-(trifluoromethyl)pyridine



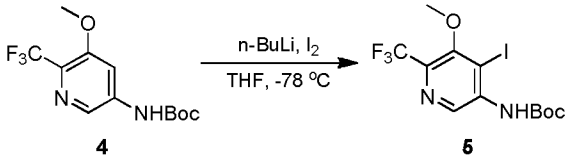
To a solution of 5-bromo-2-iodo-3-methoxy-pyridine (0.6 g, 1.91 mmol, 1 *eq*) in DMF (10 mL) was added methyl 2,2-difluoro-2-fluorosulfonyl-acetate (2.57 g, 13.38 mmol, 1.70 mL, 7 *eq*). CuI (2.55 g, 13.38 mmol, 7 *eq*) was then added under N_2. The mixture was stirred at 70 °C for 12 hr. LC-MS showed 80% of desired compound. The mixture was poured into water (100 mL), and then extracted with petroleum ether (30 mL). The organic layer was dried by Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash silica gel chromatography (0-50% ethyl acetate in petroleum ether). The fractions containing desired product (check by TLC, petroleum ether : EtOAc = 10:1, Rf = 0.8) were combined and concentrated. Compound 5-bromo-3-methoxy -2-(trifluoromethyl)pyridine (350 mg, 1.23 mmol, 64.37% yield, 90% purity) was obtained as a colorless oil. ^{1}H NMR was recorded.

Synthesis of tert-butyl N-[5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate



To a mixture of 5-bromo-3-methoxy-2-(trifluoromethyl)pyridine (350 mg, 1.37 mmol, 1 *eq*), tert-butyl carbamate (480.44 mg, 4.10 mmol, 3 *eq*) and Cs_2CO_3 (1.34 g, 4.10 mmol, 3 *eq*) in toluene (10 mL) was added $Pd_2(dba)_3$ (125.19 mg, 136.71 umol, 0.1 *eq*) and BINAP (170.25 mg, 273.42 umol, 0.2 *eq*) under N_2. The mixture was degassed with N_2 for 15 min and then stirred and refluxed at 110 °C for 12 hr. LCMS showed starting material was consumed completely. The mixture was filtered. The cake was washed with EtOAc (20 mL x 3). The combined filtrate was concentrated under reduced pressure. The resulting residues was purified by flash silica gel chromatography (0-25% ethyl acetate in petroleum ether). The fractions containing product (checked by TLC, petroleum ether : EtOAc = 8:1) were collected and concentrated. Compound tert-butyl N-[5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate (410 mg, 841.73 umol, 61.57% yield, 60% purity) was obtained as a yellow solid. ^{1}H NMR was recorded.

Synthesis of tert-butyl N-[4-iodo-5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate



4 **5**

To a solution of tert-butyl N-[5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate (262 mg, 896.48 umol, 1 *eq*) in THF (10 mL) (dried with Na and distilled freshly) was added TMEDA (312.54 mg, 2.69 mmol, 405.90 uL, 3 *eq*). The mixture was cooled to -78 °C under N_2, n-BuLi (2.5 M in n-hexane, 1.97 mL, 5.5 *eq*) was then added dropwise. After stirring at -78 °C for 1 hr, a solution of I_2 (341.30 mg, 1.34 mmol, 270.87 uL, 1.5 *eq*) in THF (3 mL) (dried with Na and distilled freshly) was added dropwise, and the mixture was stirred for 1 hr. TLC (petroleum ether : EtOAc = 5:1) showed one new spot with lower polarity. The mixture was warm to room temperature and quenched with saturated Na_2SO_3 (20 mL), the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL). The combined organic layer was dried with Na_2SO_4, and then filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography (0-15% ethyl acetate in petroleum ether). Compound tert-butyl N-[4-iodo-5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate (240 mg, 545.26 umol, 60.82% yield, 95% purity) was obtained as a white solid. ^{1}H NMR was recorded.

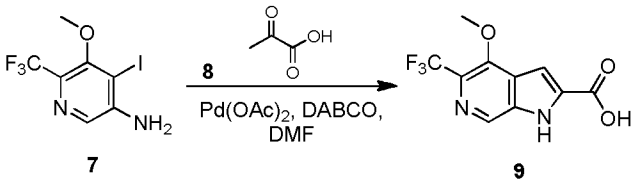
Synthesis of ethyl 4-iodo-5-methoxy-6-(trifluoromethyl)pyridin-3-amine

5 **7**

To a solution of tert-butyl N-[4-iodo-5-methoxy-6-(trifluoromethyl)-3-pyridyl]carbamate (240 mg, 573.96 umol, 1 *eq*) in DCM (1 mL) was added TFA (4.62 g, 40.52 mmol, 3 mL, 70.59 *eq*). The mixture was stirred at 20 °C for 2 hr. TLC (petroleum ether : EtOAc = 5 :1) indicated reactant was consumed completely and one new spot formed. The mixture was concentrated under reduced pressure. The residue was redissolved in EtOAc (10 mL) and washed with $NaHCO_3$ (10 mL x 3). The organic layer was dried with Na_2SO_4, and then filtered and

concentrated under reduced pressure. Compound 4-iodo-5-methoxy-6-(trifluoromethyl)pyridine -3-amine (200 mg, 565.98 umol, 98.61% yield, 90% purity) was obtained as a yellow solid. ^{1}H NMR was recorded.

Synthesis of 4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

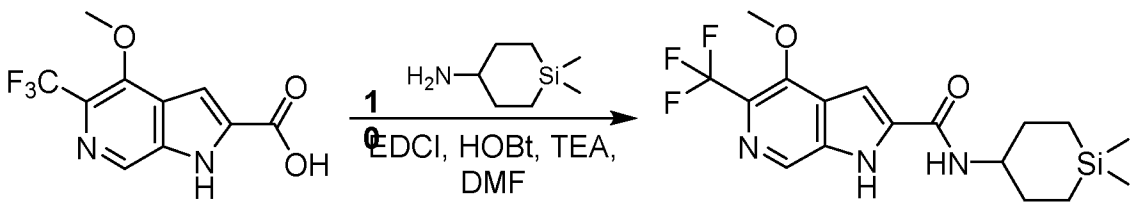


7 9

To a mixture of 4-iodo-5-methoxy-6-(trifluoromethyl)pyridin-3-amine (200 mg, 628.86 umol, 1 *eq*), 2-oxopropanoic acid (171.28 mg, 1.89 mmol, 15.16 uL, 97% purity, 3 *eq*) and DABCO (211.62 mg, 1.89 mmol, 207.47 uL, 3 *eq*) was added DMF (10 mL) (dried with CaH_2 and filtered). $Pd(OAc)_2$ (28.24 mg, 125.77 umol, 0.2 *eq*) was then added under N_2. The mixture was purged with N_2 for 15 min, and then stirred at 115 °C for 3 hr. LCMS showed one main peak with desired mass. The mixture was concentrated under reduced pressure. The residue was redissolved in MeOH and filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 39%-69%B over 11 min). Compound 4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 182.57 umol, 29.03% yield, 95% purity) was obtained as a brown solid.

LCMS (ESI) m/z 261.0 $[M+H]^+$; ^{1}H NMR (500MHz, DMSO-d_6) δ = 12.82 (br s, 1H), 8.51 (s, 1H), 7.59 - 7.51 (m, 1H), 4.25 (s, 3H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-methoxy-5-(trifluoromethyl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide



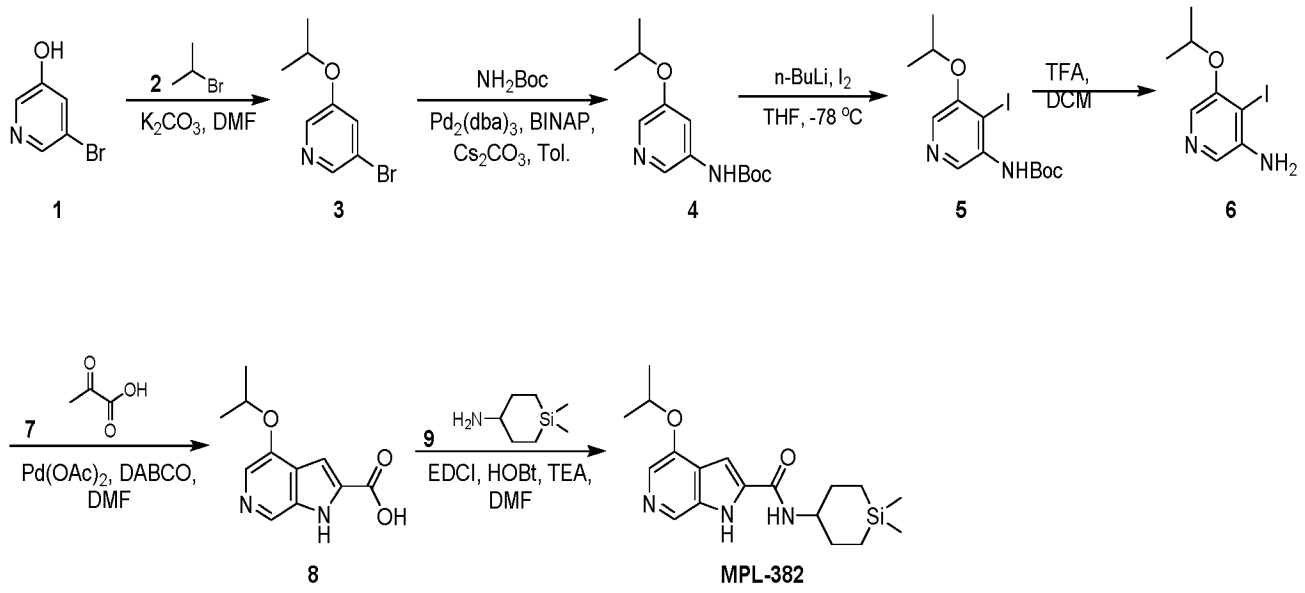
9 MPL-379

To a solution of 4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (30 mg, 115.31 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (24.87 mg, 138.37 umol, 1.2 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (44.21 mg, 230.62 umol, 2 *eq*) and HOBt (31.16 mg, 230.62 umol, 2 *eq*) in DMF (1 mL), followed with TEA (46.67 mg, 461.24 umol, 64.20 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LCMS showed one main peak with desired mass. The mixture was diluted with MeOH (2 mL) and filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient 57%-87%B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (18.1 mg, 46.96 umol, 40.72% yield, 100% purity) was obtained as a white solid.

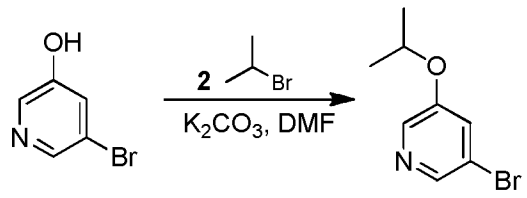
LCMS (ESI) m/z 386.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.54 (br s, 1H), 8.50 (br d, *J*=8.3 Hz, 1H), 8.43 (s, 1H), 7.67 (s, 1H), 4.20 (s, 3H), 3.79 - 3.62 (m, 1H), 1.99 (br d, *J*=9.5 Hz, 2H), 1.62 - 1.49 (m, 2H), 0.80 - 0.70 (m, 2H), 0.66 - 0.53 (m, 2H), 0.06 (s, 3H), 0.00 (s, 3H).

Example 189. MPL-382

Scheme



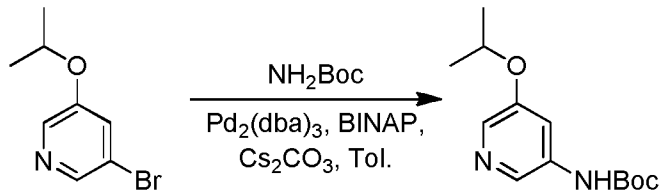
Synthesis of 3-bromo-5-isopropoxy-pyridine



1 3

To a solution of 5-bromopyridin-3-ol (2 g, 11.49 mmol, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (3.18 g, 22.99 mmol, 2 *eq*) and 2-bromopropane (2.83 g, 22.99 mmol, 2.16 mL, 2 *eq*). The mixture was stirred at 100 °C for 12 hr. TLC showed that the starting material was consumed completely, and one new spot formed. The mixture was poured into a mixture of H_2O (100 mL) and EtOAc (100 mL). Aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether). Compound 3-bromo-5-isopropoxy-pyridine (2.2 g, 9.16 mmol, 79.72% yield, 90% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of tert-butyl N-(5-isopropoxy-3-pyridyl)carbamate



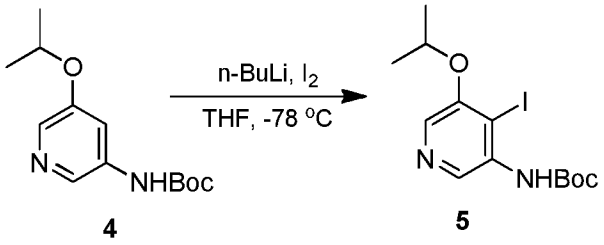
3 4

To a mixture of 3-bromo-5-isopropoxy-pyridine (2.2 g, 10.18 mmol, 1 eq) and tert-butyl carbamate (2.39 g, 20.36 mmol, 2 eq) in toluene (30 mL) was added Cs_2CO_3 (6.63 g, 20.36 mmol, 2 eq) and $Pd(dba)_2$ (585.45 mg, 1.02 mmol, 0.1 eq) and BINAP (1.27 g, 2.04 mmol, 0.2 eq) under N_2. The mixture was stirred at 110 °C for 16 hr under N_2. LCMS showed desired mass. The reaction mixture was concentrated under reduced pressure. The residue was diluted with water (50 mL), and then extracted with EtAOC (50 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-33% Ethyl acetate in petroleum ether). Compound tert-

butyl N-(5-isopropoxy-3-pyridyl) carbamate (1.1 g, 4.14 mmol, 40.68% yield, 95% purity) was obtained as a white solid.

LCMS (ESI) m/z: 253.2 $[M+H]^+$; ^1H NMR was recorded.

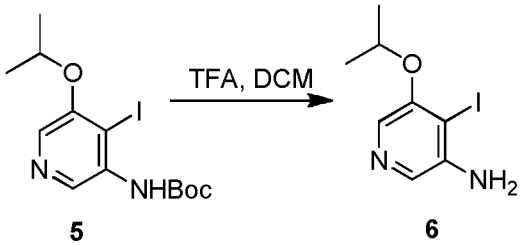
Step 3. Synthesis of tert-butyl N-(4-iodo-5-isopropoxy-3-pyridyl)carbamate



4 5

To a solution of tert-butyl N-(5-isopropoxy-3-pyridyl) carbamate (1.1 g, 4.36 mmol, 1 eq) and TMEDA (1.01 g, 8.72 mmol, 1.32 mL, 2 eq) in THF (10 mL) was added n-BuLi (2.5 M in n-hexane, 5.23 mL, 3 eq) dropwise at -78 °C under N_2. After stirring at -78 °C for 30 min, A solution of I_2 (1.66 g, 6.54 mmol, 1.32 mL, 1.5 eq) in THF (10 mL) was added dropwise at -78°C. The reaction mixture was stirred at -78 °C for another 30 min. TLC indicated a new spot was formed and some starting material remained. The reaction mixture was quenched with saturated Na_2SO_3 (30 mL) at 25°C, and then diluted with H_2O (30 mL) and extracted with EtOAc (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether).Compound tert-butyl N-(4-iodo-5-isopropoxy-3-pyridyl)carbamate (1 g, 2.12 mmol, 48.52% yield, 80% purity) was obtained as a white solid. ^1H NMR was recorded.

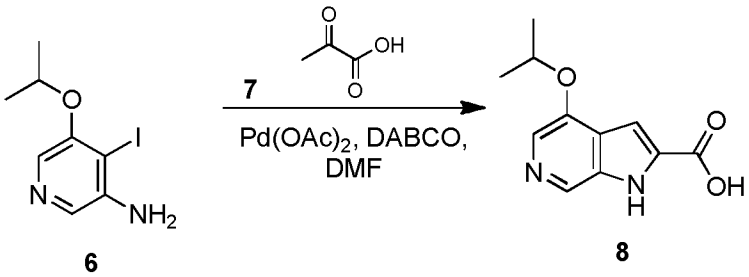
Synthesis of 4-iodo-5-isopropoxy-pyridin-3-amine



5 6

To a solution of tert-butyl N-(4-iodo-5-isopropoxy-3-pyridyl) carbamate (1.03 g, 2.73 mmol, 1 eq) in DCM (10 mL) was added TFA (15.40 g, 135.06 mmol, 10 mL, 49.47 eq). The mixture was stirred at 20 °C for 1 hr. TLC showed that reactant 5 was consumed and a new spot formed. The reaction mixture was concentrated under reduce pressure. Saturated $NaHCO_3$ (10 mL) was added to the residue and the mixture was extracted with DCM (20 mL x 2). The combined organic layer was dried with Na_2SO_4 and concentrated under reduce pressure. Compound 4-iodo-5-isopropoxy-pyridin-3-amine (650 mg, 2.10 mmol, 77.06% yield, 90% purity) was obtained as a yellow solid. ^1H NMR was recorded.

Synthesis of 4-isopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

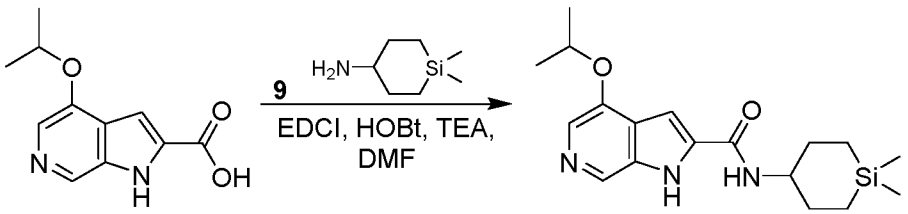


6 8

A mixture of 4-iodo-5-isopropoxy-pyridin-3-amine (300 mg, 1.08 mmol, 1 *eq*), 2-oxopropanoic acid (190.00 mg, 2.16 mmol, 152.00 uL, 2 *eq*), and DABCO (242.02 mg, 2.16 mmol, 237.28 uL, 2 *eq*) in DMF (5 mL) was degassed and purged with N_2 for 3 times. $Pd(OAc)_2$ (50 mg, 222.71 umol, 2.06e-1 *eq*) was then added. The mixture was stirred at 110 °C for 4 hr under N_2 atmosphere. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to remove DMF. The residue was diluted with toluene (30 mL). The suspension was sonicated for 30 min. The supernatant was then poured off. The residue was diluted with H_2O (10 mL), adjusted to pH to 3-4 using aqueous HCl (1 N), and filtered. The solid was collected and dried. Compound 4-isopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (100 mg, 431.38 umol, 39.99% yield, 95% purity) was obtained as a yellow solid.

LCMS m/z: 221.1 $[M+1]^+$; ^1H NMR (400MHz, METHANOL-d_4) δ = 8.70 (s, 1H), 7.95 (s, 1H), 7.40 (s, 1H), 4.97 - 4.90 (m, 1H), 1.48 (s, 3H), 1.47 (br s, 3H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-I sopropoxy-1H-pyrrolo[2,3-c]pyridine-2-c arboxamide



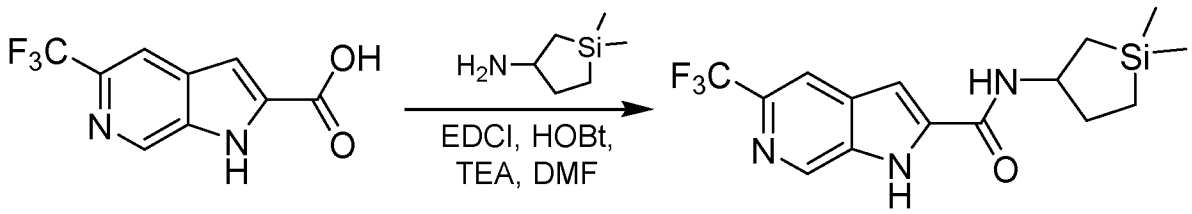
8 MPL-382

To a solution of 4-isopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (30 mg, 136.22 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (24.49 mg, 136.22 umol, 1 *eq*, HCl salt) in DMF (0.5 mL) was added a solution of HOBt (55.22 mg, 408.67 umol, 3 *eq*) and EDCI (78.34 mg, 408.67 umol, 3 *eq*) in DMF (0..5 mL), followed by TEA (82.71 mg, 817.35 umol, 113.76 uL, 6 *eq*). The mixture was stirred at 20 °C for 1 hr. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 35%-65%B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-4- isopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (9 mg, 26.05 umol, 19.12% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 346.2 $[M+H]^+$; ^1H NMR (500MHz, METHANOL-*d*4) δ = 8.46 (s, 1H), 7.78 (s, 1H), 7.30 (s, 1H), 3.83 - 3.75 (m, 1H), 2.17 - 2.10 (m, 2H), 1.73 - 1.63 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 0.88 - 0.82 (m, 2H), 0.75 - 0.68 (m, 2H), 0.13 (s, 3H), 0.05 (s, 3H).

Example 190: MPL-402

Synthesis of N-(1,1-dimethylsilolan-3-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



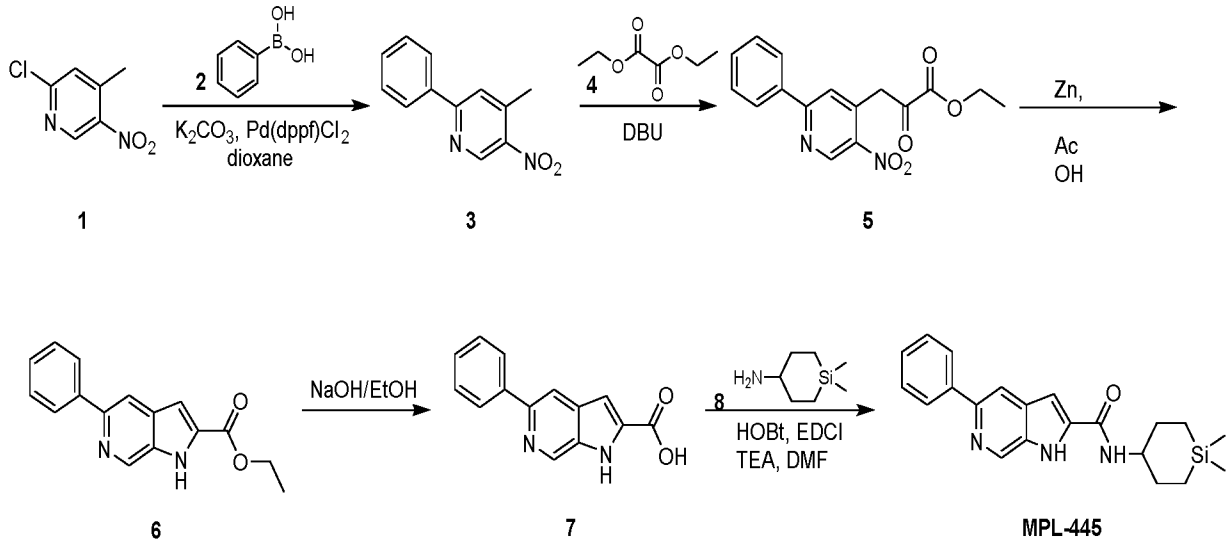
1 **MPL-402**

To a solution of 5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (30 mg, 130.35 umol, 1 *eq*) and 1,1-dimethylsilolan-3-amine (23.76 mg, 143.39 umol, 1.1 *eq*, HCl salt) in DMF (1 mL) was added a solution of EDCI (49.98 mg, 260.71 umol, 2 *eq*) and HOBt (35.23 mg, 260.71 umol, 2 *eq*), followed by TEA (52.76 mg, 521.41 umol, 72.57 uL, 4 *eq*). The mixture was stirred at 20 °C for 2 hr. LC-MS showed one main peak with desired mass. The mixture was diluted with MeOH (2 mL) and filtered to remove insoluble matter. The filtrate was purified by prep-HPLC (column: YMC-Actus Triart C18 150*30mm*5um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 56%-86%B over 11min. Compound N-(1,1-dimethylsilolan-3-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (21.2 mg, 62.10 umol, 47.64% yield, 100% purity) was obtained as a white solid.

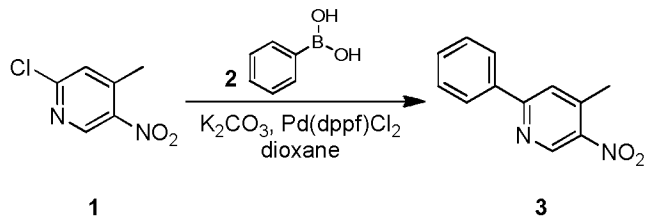
LCMS (ESI) m/z 342.0 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.34 (s, 1H), 8.69 (s, 1H), 8.50 (br d, *J*=7.8 Hz, 1H), 8.03 (s, 1H), 7.19 (s, 1H), 3.95 - 3.81 (m, 1H), 1.95 - 1.80 (m, 1H), 1.28 (dq, *J*=7.1, 12.1 Hz, 1H), 1.01 - 0.90 (m, 1H), 0.72 - 0.58 (m, 1H), 0.50 (dd, *J*=11.4, 14.1 Hz, 1H), 0.42 - 0.26 (m, 1H), 0.00 (s, 6H).

Example 191. MPL-445

Scheme



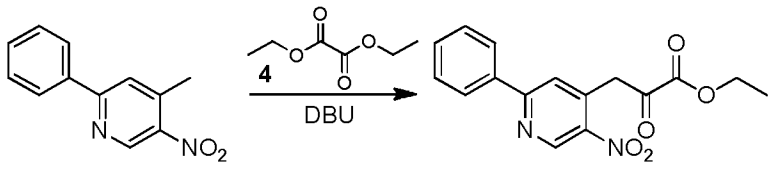
Synthesis of 4-methyl-5-nitro-2-phenyl-pyridine



To a mixture of 2-chloro-4-methyl-5-nitro-pyridine (5 g, 28.97 mmol, 1 eq), phenylboronic acid (4.3 g, 35.27 mmol, 1.22 eq) and K_2CO_3 (8.01 g, 57.95 mmol, 2 eq) was added dioxane (50 mL) and H_2O (1 mL). The mixture was purged with N_2 and then $Pd(dppf)Cl_2.CH_2Cl_2$ (2.37 g, 2.90 mmol, 0.1 eq) was added under N_2. The mixture was stirred at 110 °C for 12 hr. LCMS showed desired mass. The mixture was filtered. The cake was washed with EtOAc (50 mL x 2). The combined filtrate was dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0-3% ethyl acetate in petroleum ether). Compound 4-methyl-5-nitro-2-phenyl-pyridine (4 g, 15.87 mmol, 54.78% yield, 85% purity) was obtained as a red solid.

LCMS (ESI) m/z 215.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of ethyl 3-(5-nitro-2-phenyl-4-pyridyl)-2-oxo-propanoate

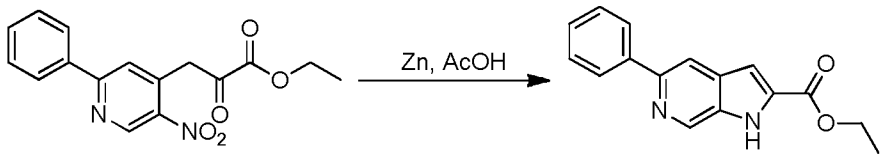


3 5

To a solution of 4-methyl-5-nitro-2-phenyl-pyridine (1 g, 4.67 mmol, 1 eq) in diethyl oxalate (10.70 g, 73.22 mmol, 10 mL, 15.68 eq) was added DBU (2.84 g, 18.67 mmol, 2.81 mL, 4 eq). The mixture was stirred at 40 °C for 12 hr. LCMS showed desired mass. The residue was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-10% ethyl acetate in petroleum ether). Compound ethyl 3-(5-nitro-2-phenyl-4-pyridyl)-2-oxo-propanoate (683 mg, 1.74 mmol, 37.24% yield, 80% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 315.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of ethyl 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

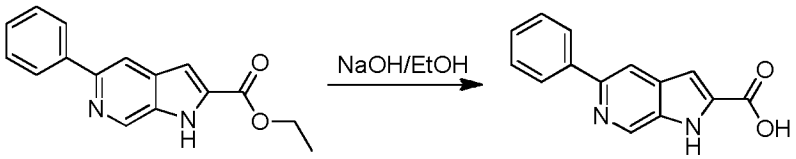


5 6

To a solution of ethyl 3-(5-nitro-2-phenyl-4-pyridyl)-2-oxo-propanoate (800 mg, 2.55 mmol, 1 eq) in THF (10 mL) was added Zn (1.66 g, 25.45 mmol, 10 eq) and AcOH (764.28 mg, 12.73 mmol, 727.89 uL, 5 eq). The mixture was stirred at 75 °C for 2 hr. LCMS showed desired mass. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-5% methanol in dichloromethane). Compound Ethyl 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (328 mg, 985.38 umol, 38.71% yield, 80% purity) was obtained as a yellow solid.

LCMS (ESI) m/z 267.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

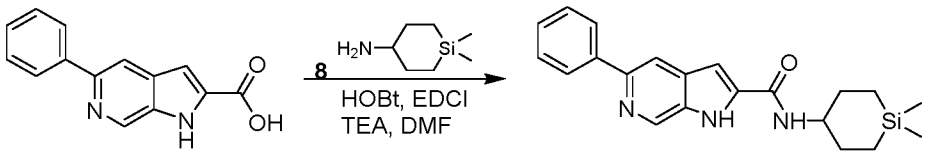


6 7

To a solution of ethyl 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (50 mg, 187.76 umol, 1 eq) in EtOH (2 mL) was added NaOH (2 M, 2 mL, 21.30 eq). The mixture was stirred at 80 °C for 12 hr. LCMS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was diluted with water (20 mL), adjusted to pH to 2 using aqueous HCl (2 M), and then extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 134.32 umol, 71.54% yield, 80% purity) was obtained as a yellow solid, which was used for the next step without further purification.

LCMS (ESI) m/z 239.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-*d*6) δ = 13.10 (br s, 1H), 8.99 (s, 1H), 8.43 (s, 1H), 8.11 - 8.02 (m, 2H), 7.60 - 7.45 (m, 3H), 7.32 (s, 1H).

N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide



7 MPL-445

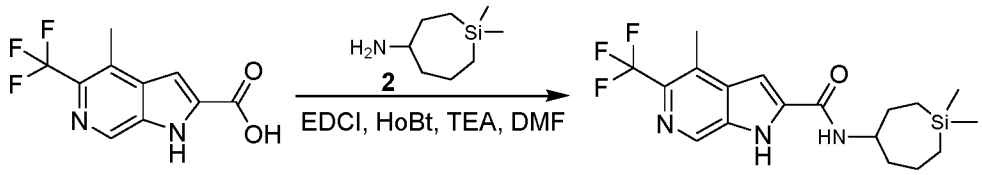
To a solution of 5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (40 mg, 167.90 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (33.20 mg, 184.69 umol, 1.1 eq, HCl salt) in DMF (1 mL) was added a solution of HOBt (68.06 mg, 503.69 umol, 3 eq) and EDCI (96.56 mg, 503.69 umol, 3 eq) in DMF (1 mL) with stirring, followed by TEA (84.95 mg, 839.49 umol, 116.85 uL, 5 eq) The mixture was stirred at 25 °C for 2 hr. LCMS showed desired mass. The mixture was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225%

formic acid in water, B: CH_3CN; gradient: 28%-59%B over 11 min). Compound N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (34.3 mg, 87.75 umol, 52.26% yield, 93% purity) was obtained as a white solid.

LCMS (ESI) m/z 364.2 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d6) δ = 12.29 (br s, 1H), 8.86 (s, 1H), 8.58 (br s, 1H), 8.26 (br d, *J*=8.2 Hz, 1H), 8.12 - 7.96 (m, 2H), 7.58 - 7.22 (m, 4H), 3.75 (br d, *J*=8.5 Hz, 1H), 2.10 - 1.95 (m, 2H), 1.73 - 1.53 (m, 2H), 0.87 - 0.56 (m, 4H), 0.17 - -0.03 (m, 6H).

Example 192. MPL-451

Synthesis of N-(1, 1-dimethylsilepan-4-yl) -4-methyl-5-(trifluoromethyl) -1H-pyrrolo [2,3-c] pyridine-2-carboxamide



1 **MPL-451**

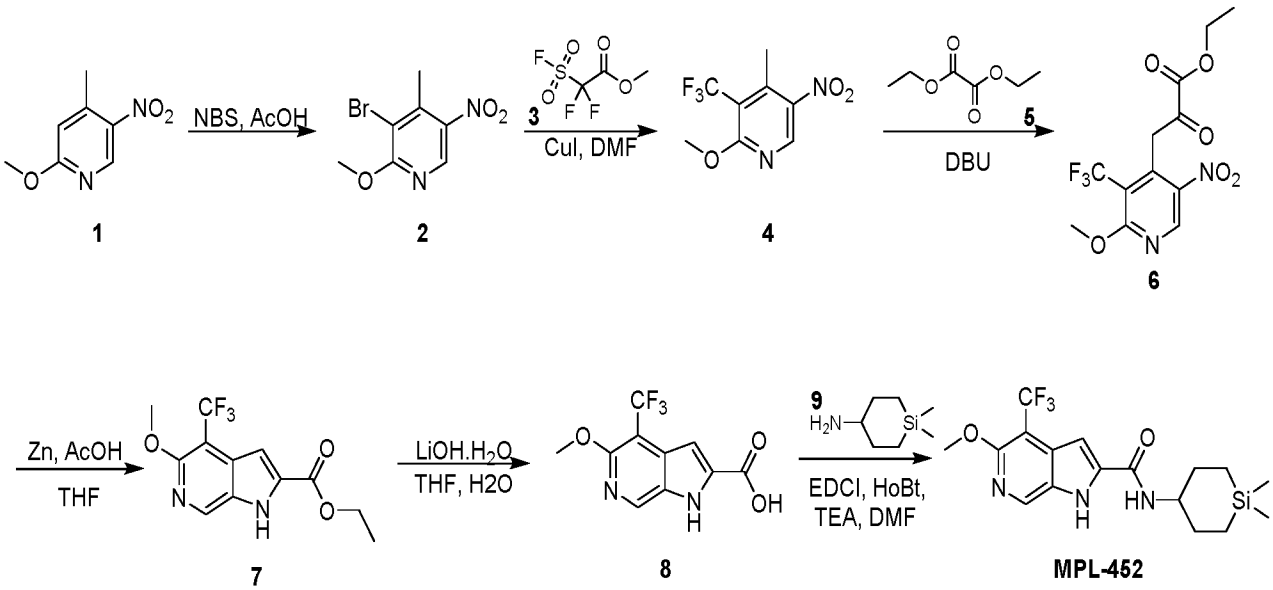
To a solution of 4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 204.78 umol, 1 eq) and 1,1-dimethylsilepan-4-amine (47.62 mg, 245.73 umol, 1.2 eq, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (117.77 mg, 614.33 umol, 3 eq) and HOBt (83.01 mg, 614.33 umol, 3 eq) in DMF (1.5 mL), followed by TEA (103.61 mg, 1.02 mmol, 142.51 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient: 53%-83% B over 11 min). Compound N-(1, 1-dimethylsilepan-4-yl) -4-methyl-5-(trifluoromethyl) -1H-pyrrolo [2,3-c] pyridine-2-carboxamide (24.9 mg, 64.66 umol, 31.57% yield, 99.6% purity) was obtained as a white solid.

LCMS m/z: 384.2 $[M+1]^+$; ^1H NMR (400MHz, DMSO-d_6) δ = 12.43 (br s, 1H), 8.67 (s, 1H), 8.59 (br d, *J*=8.1 Hz, 1H), 7.49 (s, 1H), 4.01 - 3.85 (m, 1H), 2.64 (d, *J*=2.0 Hz, 3H), 2.00 - 1.77

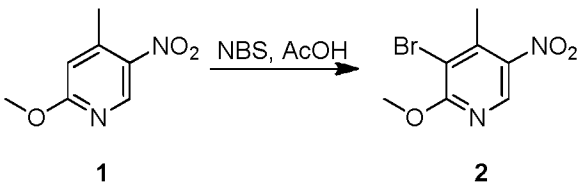
(m, 3H), 1.76 - 1.63 (m, 1H), 1.59 - 1.41 (m, 2H), 0.85 - 0.69 (m, 2H), 0.69 - 0.56 (m, 2H), 0.04 (d, *J*=9.3 Hz, 6H).

Example 193: MPL-452

Scheme



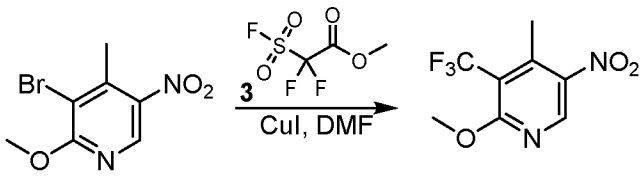
Synthesis of 3-bromo-2-methoxy-4-methyl-5-nitro-pyridine



To a solution of 2-methoxy-4-methyl-5-nitro-pyridine (19.61 g, 116.62 mmol, 1 eq) in AcOH (200 mL) was added NBS (83.03 g, 466.49 mmol, 4 eq) under N_2 atmosphere. The suspension was degassed and purged with N_2 for 3 times, and then stirred under N_2 at 110 °C for 18 hr. LCMS showed desired mass. The reaction mixture was poured into ice water (1200 mL), then filtered. The cake was collected and dried under reduced pressure. Compound 3-bromo-2-methoxy-4-methyl-5-nitro-pyridine (18 g, crude) was obtained as a yellow solid.

LCMS (ESI) m/z: 248.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 2-methoxy-4-methyl-5-nitro-3- (trifluoromethyl) pyridine

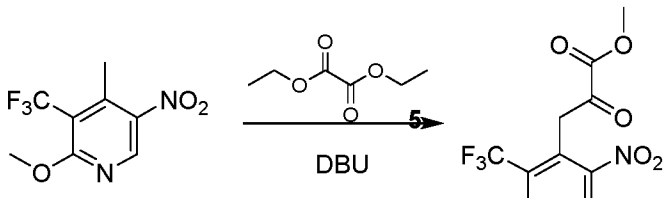


2 4

To a solution of 3-bromo-2-methoxy-4-methyl-5-nitro-pyridine (17 g, 68.81 mmol, 1 eq) in DMF (200 mL) was added CuI (52.42 g, 275.25 mmol, 4 eq) and methyl 2,2-difluoro-2-fluorosulfonyl-acetate (85.00 g, 442.47 mmol, 56.29 mL, 6.43 eq). The mixture was stirred at 100 °C for 5 hr. LCMS showed desired mass. The reaction was poured in saturated $NaHCO_3$ (500 mL), and then extracted with EtOAC (120 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-2% ethyl acetate in petroleum ether). Compound 2-methoxy-4-methyl-5-nitro-3-(trifluoromethyl) pyridine (15 g, 47.64 mmol, 69.23% yield, 75% purity) was obtained as a yellow oil.

LCMS (ESI) m/z: 238.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO) was recorded.

Synthesis of ethyl 3-[2-methoxy-5-nitro-3-(trifluoromethyl)-4-pyridyl]-2-oxo-propanoate



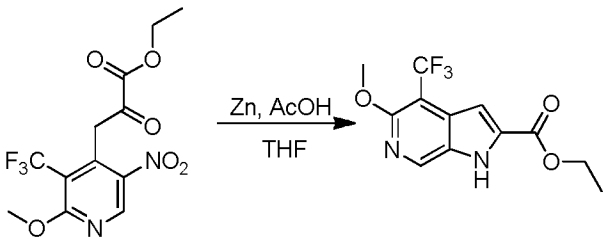
4 6

To a solution of 2-methoxy-4-methyl-5-nitro-3-(trifluoromethyl)pyridine (1 g, 4.23 mmol, 1 eq) in diethyl oxalate (10.70 g, 73.22 mmol, 10 mL, 17.29 eq) was added DBU (2.58 g, 16.94 mmol, 2.55 mL, 4 eq). The mixture was stirred at 40 °C for 12 hr. LCMS showed desired mass. The residue was diluted with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine (50 mL x 2), dried over Na_2SO_4, and filtered and

concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-10% ethyl acetate in petroleum ether). Compound ethyl 3-[2-methoxy-5-nitro-3-(trifluoromethyl)-4-pyridyl]-2-oxo-propanoate (1.22 g, crude) was obtained as a yellow oil, which was used for the next step without further purification.

LCMS (ESI) m/z: 337.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of ethyl 5-methoxy-4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxylate

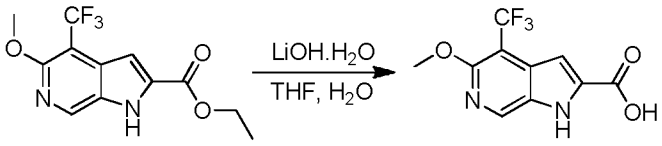


6 7

To a solution of ethyl 3-[2-methoxy-5-nitro-3-(trifluoromethyl)-4-pyridyl]-2-oxo-propanoate (1.22 g, 3.63 mmol, 1 eq) in THF (10 mL) was added Zn (2.37 g, 36.29 mmol, 10 eq) and AcOH (1.09 g, 18.14 mmol, 1.04 mL, 5 eq). The mixture was stirred at 70 °C for 4 hr. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was purified by column chromatography (SiO_2, 0-33% ethyl acetate in petroleum ether). Compound Ethyl 5-methoxy-4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (500 mg, 520.43 umol, 14.34% yield, 30% purity) was obtained as a white solid.

LCMS (ESI) m/z: 289.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 5-methoxy-4- (trifluoromethyl)- 1H-pyrrolo[2,3-c] pyridine-2-carboxylic acid



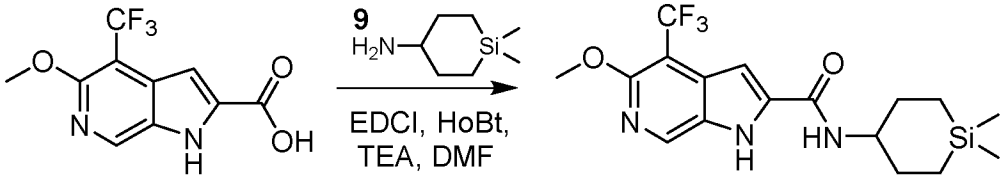
7 8

To a solution of ethyl 5-methoxy-4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (500 mg, 871.03 umol, 50.21% purity, 1 eq) in THF (3 mL) was added a solution of $LiOH.H_2O$

(219.31 mg, 5.23 mmol, 6 eq) in H_2O (3 mL). The mixture was stirred at 80 °C for 2 hr. LC-MS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove THF (3 mL). The aqueous phase was adjusted to pH to 3-4 with aqueous HCl (6 N) and then purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient; 32%-62% B over 11 min). Compound 5-methoxy-4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (53 mg, 193.53 umol, 22.22% yield, 95% purity) was obtained as a brown solid.

LCMS (ESI) m/z: 261.2 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of N-(1,1 -dimethylsilinan-4-yl) -5-methoxy-4- (trifluoromethyl) -1H-pyrrolo [2,3-c] pyridine-2-carboxamide



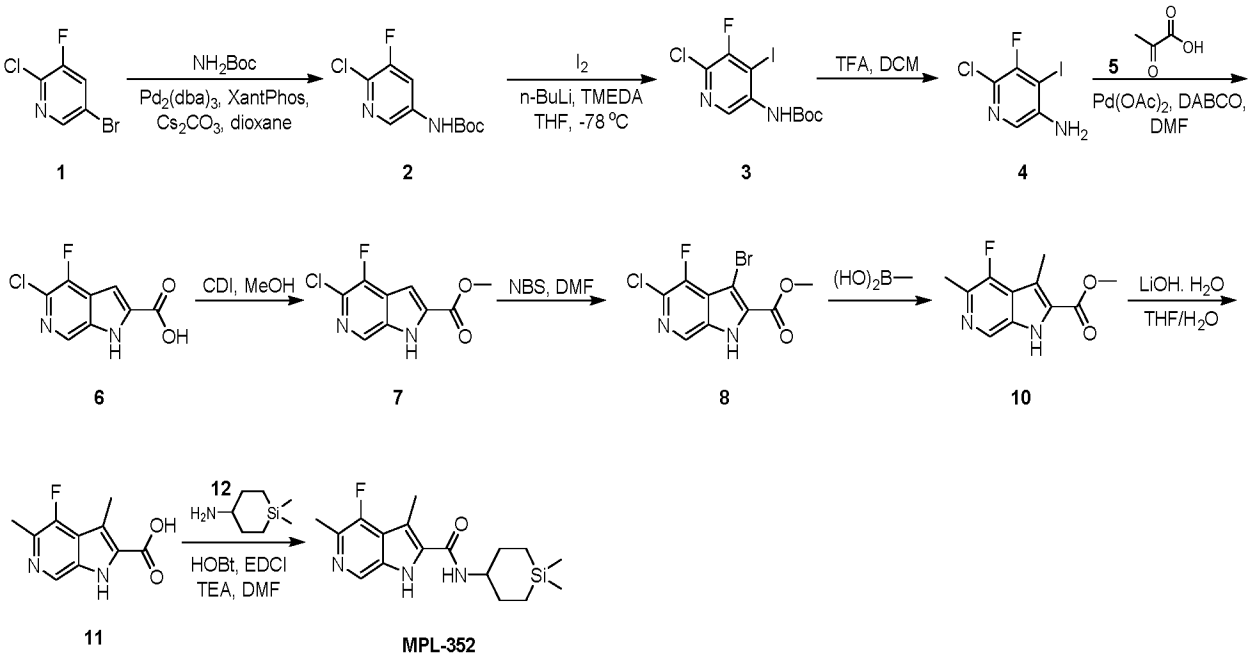
8 **MPL-452**

To a solution of 5-methoxy-4-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 192.18 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (41.46 mg, 230.62 umol, 1.2 eq, HCl salt) in DMF (2 mL) was added a solution of EDCI (110.53 mg, 576.55 umol, 3 eq) and HOBt (77.90 mg, 576.55 umol, 3 eq) in DMF (1 mL), followed by TEA (97.23 mg, 960.91 umol, 133.75 uL, 5 eq).The mixture was stirred at 25 °C for 1 hr. LCMS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18 150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN, gradient: 63%-93% B over 11 min). Compound N-(1,1 -dimethylsilinan-4-yl) -5-methoxy-4-(trifluoromethyl) -1H-pyrrolo [2,3-c] pyridine-2-carboxamide (25.6 mg, 66.26 umol, 34.48% yield, 99.8% purity) was obtained as a white solid.

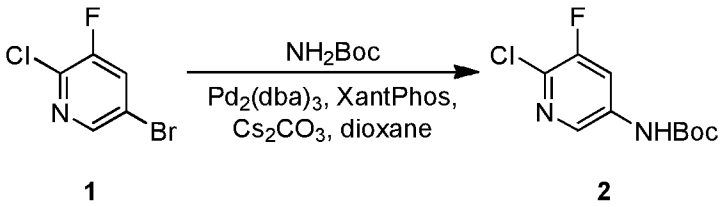
LCMS m/z: 386.1 $[M+1]^+$; ^{1} H NMR (500MHz, DMSO-d6) δ = 12.27 (s, 1H), 8.69 - 8.53 (m, 2H), 7.26 (d, *J*=1.7 Hz, 1H), 3.96 (s, 3H), 3.77 - 3.68 (m, 1H), 2.05 - 1.94 (m, 2H), 1.67 - 1.52 (m, 2H), 0.78 (br d, *J*=14.5 Hz, 2H), 0.62 (dt, *J*=4.8, 14.2 Hz, 2H), 0.09 (s, 3H), 0.03 (s, 3H).

Example 194. MPL-352

Scheme



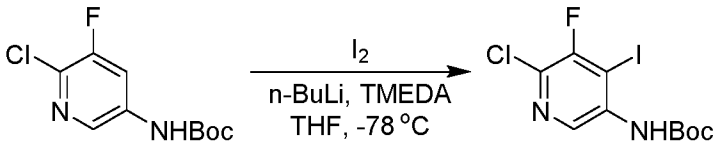
Step 1. Synthesis of tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate



A mixture of 5-bromo-2-chloro-3-fluoro-pyridine (10 g, 47.52 mmol, 1 *eq*), tert-butyl carbamate (6.68 g, 57.03 mmol, 1.2 *eq*), Xantphos (824.90 mg, 1.43 mmol, 0.03 *eq*) and Cs_2CO_3 (30.97 g, 95.04 mmol, 2 *eq*) in dioxane (15 mL) was degassed and purged with N_2 for 3 times, then $Pd_2(dba)_3$ (1.31 g, 1.43 mmol, 0.03 *eq*) was added. The reaction mixture was stirred at 85 °C for 12 hr under N_2 atmosphere. LCMS indicated desired mass. The mixture was filtered. The filtrate was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether). Compound tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (6.5 g, 25.03 mmol, 47.89% yield, 95% purity) was obtained as a pale-orange solid.

LCMS (ESI) m/z: 247.0 $[M+H]^+$; ^1H NMR was recorded.

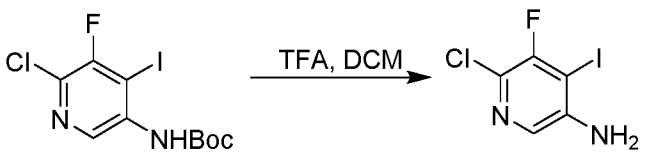
Synthesis of tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate



2 **3**

To a solution of tert-butyl N-(6-chloro-5-fluoro-3-pyridyl)carbamate (1 g, 4.05 mmol, 1 *eq*) and TMEDA (942.21 mg, 8.11 mmol, 1.22 mL, 2 *eq*) in THF (12 mL) was added n-BuLi (2.5 M in n-hexane, 4.05 mL, 2.5 *eq*) dropwise at -78 °C under N_2. After stirring at -78 °C for 30 min, a solution of I_2 (1.54 g, 6.08 mmol, 1.22 mL, 1.5 *eq*) in THF (5 mL) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 min. TLC (petroleum ether : ethyl acetate = 3:1) indicated compound 2 was consumed completely and one new spot formed. The reaction mixture was quenched with saturated Na_2SO_3 (20 mL) at 25 °C, and then diluted with H_2O (10 mL) and extracted with EtOAc (30 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-10% ethyl acetate in petroleum ether). Compound tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate (1.27 g, 3.24 mmol, 79.88% yield, 95% purity) was obtained as a white solid. ^1H NMR was recorded.

Synthesis of 6-chloro-5-fluoro-4-iodo-pyridin-3-amine



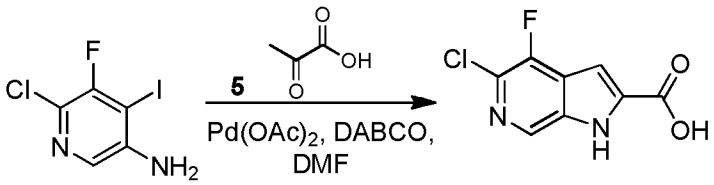
3 **4**

To a solution of tert-butyl N-(6-chloro-5-fluoro-4-iodo-3-pyridyl)carbamate (8.68 g, 23.30 mmol, 1 *eq*) in DCM (10 mL) was added TFA (47.74 g, 418.69 mmol, 31.00 mL, 17.97 *eq*). The mixture was stirred at 30 °C for 12 hr. LCMS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was dissolved in saturated

$NaHCO_3$ (5 mL), and then extracted with ethyl acetate (15 mL x 2). The combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-20% ethyl acetate in petroleum ether). Compound 6-chloro-5-fluoro-4-iodo-pyridin-3-amine (6.26 g, 21.83 mmol, 81.47% yield, 95% purity) was obtained as a white solid.

LCMS (ESI) m/z: 272.9 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

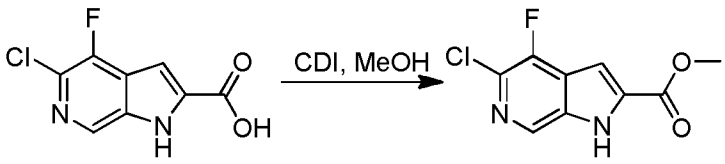


4 **6**

A mixture of 6-chloro-5-fluoro-4-iodo-pyridin-3-amine (6.26 g, 22.98 mmol, 1 *eq*), 2-oxopropanoic acid (4.05 g, 45.95 mmol, 3.24 mL, 2 *eq*) and DABCO (5.15 g, 45.95 mmol, 5.05 mL, 2 *eq*) in DMF (50 mL) was degassed and purged with N_2 for 3 times, $Pd(OAc)_2$ (515.85 mg, 2.30 mmol, 0.1 *eq*) was then added. The mixture was stirred at 110 °C for 4 hr under N_2 atmosphere. LC-MS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with toluene (50 mL), sonicated for 30 minutes and filtered. The filter cake was suspended in CH_3CN and filtered. The cake was collected and dried under reduced pressure. Compound 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (5 g, crude) was obtained as a brown solid, which was used for the next step without further purification.

LCMS (ESI) m/z: 215.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate

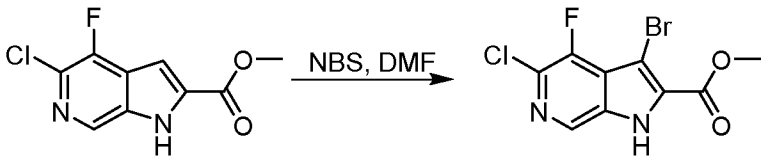


7

A solution of 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (1.29 g, 6.01 mmol, 1 *eq*) and CDI (1.07 g, 6.61 mmol, 1.1 *eq*) in DMF (10 mL) was stirred at 30 °C for 1 hr. MeOH (9.50 g, 296.54 mmol, 12 mL, 49.33 *eq*) was then added. The mixture was stirred at 30 °C for 1 hr. LCMS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove MeOH and then poured into H_2O (100 mL), the suspension was filtered. The aqueous filtrate was extracted with a mixed solvent of dichloromethane and methanol (10:1) (50 mL x 3). The solid was then dissolved in the combined organic phase, which was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compound methyl 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (1.1 g, 3.85 mmol, 64.03% yield, 80% purity) was obtained as a brown solid. The crude product was used for the next step without further purification.

LCMS (ESI) m/z: 229.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of Compound methyl 3-bromo-5-chloro-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2 - carboxylate



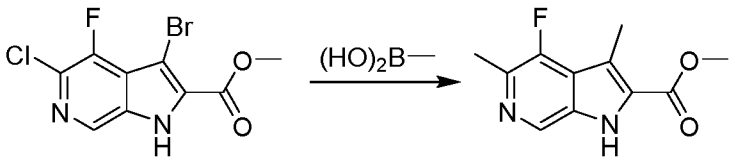
7 8

A mixture of methyl 5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (500 mg, 2.19 mmol, 1 *eq*) and NBS (428.21 mg, 2.41 mmol, 1.1 *eq*) in DMF (10 mL) under N_2 was stirred at 30 °C for 3 hr. LC-MS showed desired mass. The mixture was poured into water (100 mL) and the suspension was filtered. The filter cake was washed with water (50 mL), collected and dried in vacuo. Compound methyl 3-bromo-5-chloro-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2 -

carboxylate (459 mg, 1.34 mmol, 61.42% yield, 90% purity) was obtained as a brown solid. The crude product was used for the next step without further purification.

LCMS (ESI) m/z: 309.0 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of methyl 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxylate

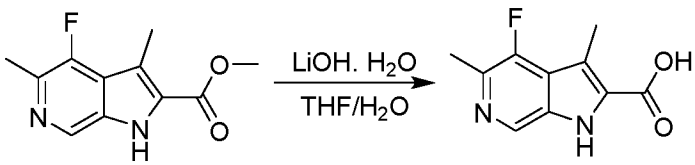


8 **10**

A mixture of methyl 3-bromo-5-chloro-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (600 mg, 1.95 mmol, 1 *eq*), methylboronic acid (583.99 mg, 9.76 mmol, 5 *eq*), K_3PO_4 (1.24 g, 5.85 mmol, 3 *eq*) and XPhos (186.04 mg, 390.24 umol, 0.2 *eq*) in dioxane (4 mL) was de-gassed under N_2 atmosphere. $Pd_2(dba)_3$ (357.35 mg, 390.24 umol, 0.2 *eq*) was then added. The suspension was degassed and purged with N_2 for 3 times, and stirred under N_2 at 120 °C for 12 hr. LCMS showed desired mass. EtOAc (30 mL) was added. The mixture was filtered to remove the insoluble materials. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0-100% ethyl acetate in petroleum ether). Compound methyl 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxylate (170 mg, 650.27 umol, 28.73% yield, 85% purity) was obtained as a yellow solid.

LCMS (ESI) m/z: 223.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 4- fluoro-3,5–dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid

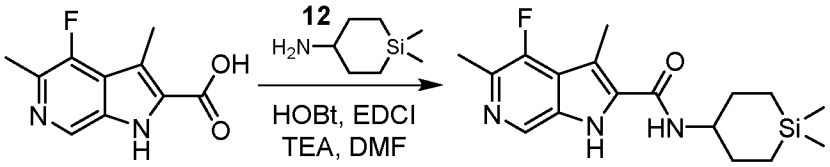


10 **11**

To a solution of methyl 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylate (170 mg, 765.02 umol, 1 *eq*) in THF (2 mL) was added a solution of $LiOH.H_2O$ (192.62 mg, 4.59 mmol, 6 *eq*) in H_2O (2 mL). The mixture was stirred at 80 °C for 12 hr. LC-MS showed desired mass. The reaction mixture was concentrated under reduced pressure to remove THF (2 mL). The aqueous solution was adjusted to pH to 3-4 with aqueous HCl (1 N) and then filtered. The cake was collected, washed with petroleum ether (15 mL), and dried under reduced pressure. Compound 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxylic acid (102 mg, 440.95 umol, 57.64% yield, 90% purity) was obtained as a yellow solid, which was used for the next step without further purification.

LCMS (ESI) m/z: 209.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 12.01 (s, 1H), 8.48 (s, 1H), 2.62 (s, 3H), 2.44 (d, *J*=3 Hz, 3H).

Synthesis of N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide



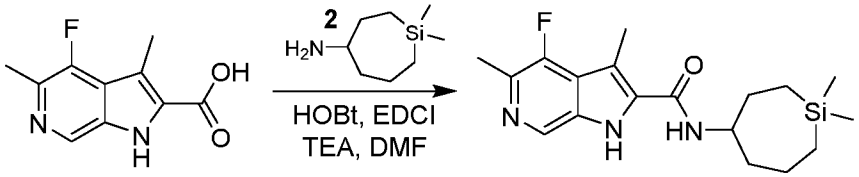
11 **MPL-352**

To a solution of 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 240.17 umol, 1 *eq*) and 1,1-dimethylsilinan-4-amine (51.81 mg, 288.20 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (138.12 mg, 720.50 umol, 3 *eq*) and HOBt (97.36 mg, 720.50 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (145.81 mg, 1.44 mmol, 200.57 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS showed desired mass. The reaction mixture was filtered. The residue was purified by prep-HPLC (column: Agela DuraShell C18 150*25mm*5um; mobile phase: A: 0.04% NH_3H_2O and 10mM of NH_4HCO_3 in water, B: CH_3CN; gradient: 49% -79%B over 10 min). Compound N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,5-dimethyl -1H-pyrrolo [2,3-c] pyridine-2-carboxamide (24.7 mg, 74.07 umol, 30.84% yield, 100% purity) was obtained as a white solid.

LCMS (ESI) m/z: 334.1 $[M+H]^+$; ^1H NMR (500MHz, DMSO-d_6) δ = 8.47 (d, *J*=2.3 Hz, 1H), 8.00 (d, *J*=7.9 Hz, 1H), 3.77 - 3.67 (m, 1H), 2.54 (s, 3H), 2.44 (d, *J*=3.2 Hz, 3H), 2.07 - 1.96 (m, 2H), 1.70 - 1.53 (m, 2H), 0.83 - 0.71 (m, 2H), 0.61 (dt, *J*=4.7, 13.8 Hz, 2H), 0.10 - 0.00 (m, 6H).

Example 195. MPL-353

Synthesis of N-(1,1-dimethylsilepan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo [2,3-c] pyridine-2-carboxamide



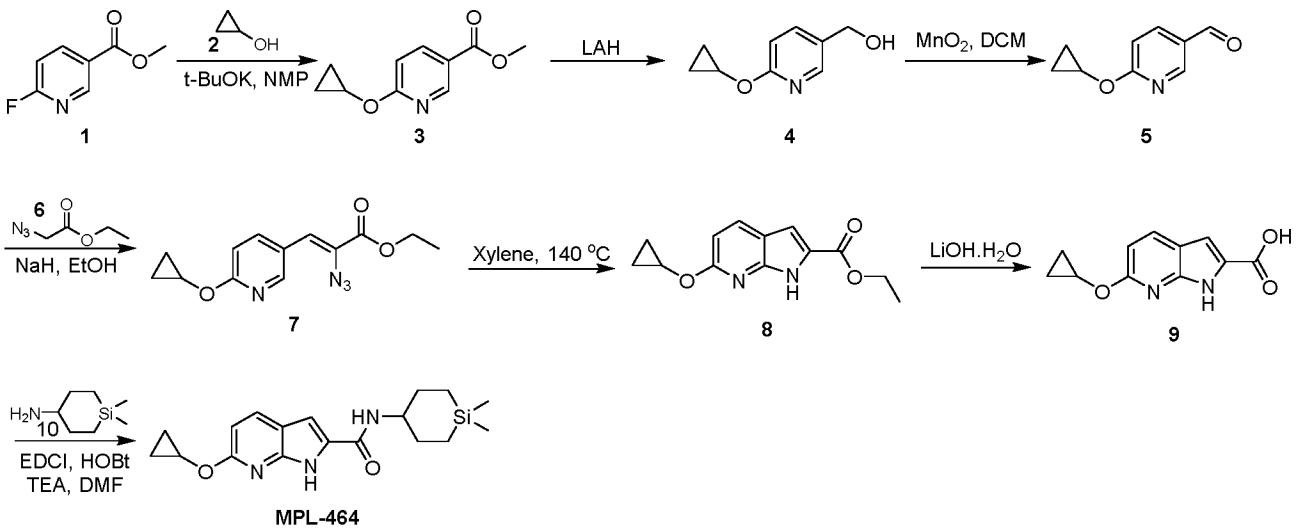
1 **MPL-353**

To a solution of 4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxylic acid (50 mg, 240.17 umol, 1 *eq*) and 1,1-dimethylsilepan-4-amine (55.85 mg, 288.20 umol, 1.2 *eq*, HCl salt) in DMF (1.5 mL) was added a solution of EDCI (138.12 mg, 720.51 umol, 3 *eq*) and HOBt (97.36 mg, 720.51 umol, 3 *eq*) in DMF (0.5 mL), followed by TEA (145.82 mg, 1.44 mmol, 200.57 uL, 6 *eq*). The mixture was stirred at 25 °C for 1 hr. LCMS indicated desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column, Agela DuraShell C18 150*25mm*5um; mobile phase: A: 0.04% NH_3H_2O and 10mM of NH_4HCO_3 in water, B: CH_3CN; gradient: 51% -81%B over 10 min). Compound N-(1,1-dimethylsilepan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide (23.3 mg, 66.92 umol, 27.86% yield, 99.806% purity) was obtained as a white solid.

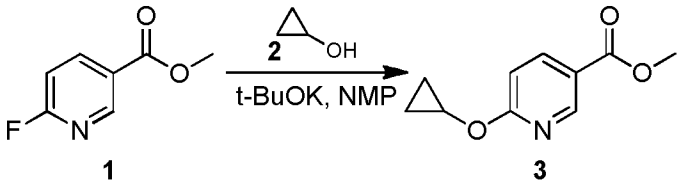
LCMS m/z: 348.1 $[M+1]^+$; ^1H NMR (500MHz, DMSO-d_6) *δ* = 11.79 (br s, 1H), 8.47 (d, *J*=2.3 Hz, 1H), 8.06 (d, *J*=7.6 Hz, 1H), 3.93 - 3.84 (m, 1H), 2.54 (s, 3H), 2.44 (d, *J*=3.4 Hz, 3H), 2.01 - 1.75 (m, 3H), 1.68 (dq, *J*=2.0, 11.5 Hz, 1H), 1.56 - 1.41 (m, 2H), 0.84 - 0.69 (m, 2H), 0.67 - 0.53 (m, 2H), 0.03 (d, *J*=3.4 Hz, 6H).

Example 196. MPL-464

Scheme



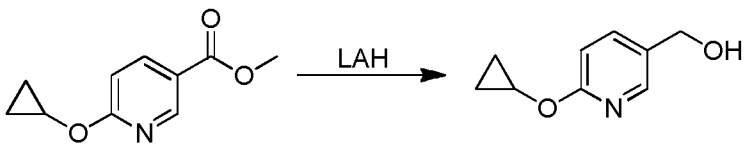
Synthesis of methyl 6-(cyclopropoxy) pyridine-3-carboxylate



To a solution of methyl 6-fluoropyridine-3-carboxylate (500 mg, 3.22 mmol, 1 eq) in NMP (10 mL) was added cyclopropanol (224.64 mg, 3.87 mmol, 1.2 eq). The mixture was stirred at 0 °C for 5 min. t-BuOK (723.36 mg, 6.45 mmol, 2 eq) was then added dropwise at 0 °C. The mixture was stirred at 25 °C for 12 hr. LC-MS showed desired mass. The reaction mixture was poured into a mixed solvent of petroleum ether/ Ethyl acetate/H_2O (20 mL / 20mL / 40 mL). The organic layer was washed with 5% of aqueous solution LiCl (20 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0-20% Ethyl acetate in petroleum ether). Compound methyl 6-(cyclopropoxy) pyridine-3-carboxylate (250 mg, 1.04 mmol, 32.12% yield, 80% purity) was obtained as a white solid.

LCMS (ESI) m/z: 194.1 $[M+H]^+$; ^1H NMR was recorded.

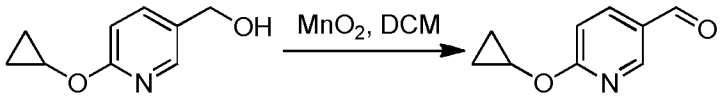
Synthesis of [6-(cyclopropoxy)-3-pyridyl] methanol



3 4

To an ice-cooled solution of methyl 6-(cyclopropoxy) pyridine-3-carboxylate (1.3 g, 6.73 mmol, 1 eq) in dried THF (12 mL) was added LAH (383.08 mg, 10.09 mmol, 1.5 eq) in batches. The mixture was stirred at 0 °C for 1 hr. TLC (Petroleum ether : Ethyl acetate=10:1) indicated compound 3 was consumed completely and one new spot formed. The reaction was quenched with water (0.383 mL), NaOH (15%, 0.383 mL) and water (1.149 mL). The mixture was dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-100% Ethyl acetate in petroleum ether). Compound [6-(cyclopropoxy)-3-pyridyl] methanol (800 mg, 3.87 mmol, 57.58% yield, 80% purity) was obtained as a brown oil. ^1H NMR was recorded.

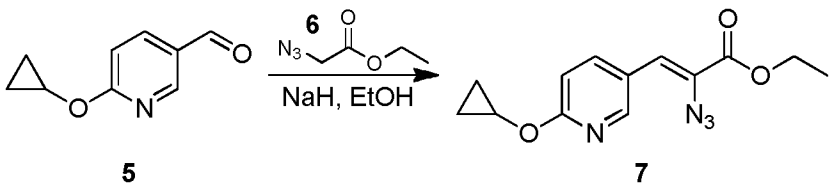
Synthesis of 6-(cyclopropoxy) pyridine-3-carbaldehyde



4 5

To a solution of [6-(cyclopropoxy)-3-pyridyl] methanol (800 mg, 4.84 mmol, 1 eq) in DCM (10 mL) was added MnO_2 (4.21 g, 48.43 mmol, 10 eq). The mixture was stirred at 25 °C for 12 hr. TLC (Petroleum ether : Ethyl acetate=5:1) indicated compound 4 was consumed completely, and a new spot was detected. The reaction mixture was filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-20% Ethyl acetate in petroleum ether). Compound 6-(cyclopropoxy) pyridine-3-carbaldehyde (733 mg, 3.59 mmol, 74.21% yield, 80% purity) was obtained as a colorless oil. ^1H NMR was recorded.

Step 4. Synthesis of ethyl (Z)-2-azido-3- [6-(cyclopropoxy)-3-pyridyl] prop-2-enoate

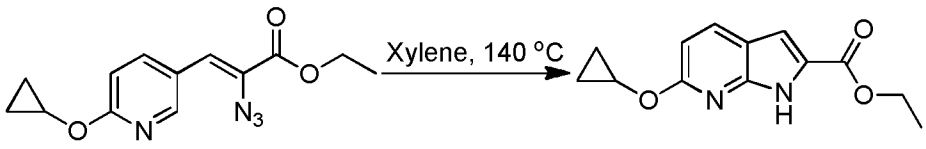


5 7

NaH (539.01 mg, 13.48 mmol, 60% purity, 3 eq) was added to EtOH (10 mL) in batches. The mixture was stirred at 20 °C to a clear solution then cooled to -10 °C. Then a solution of 6-(cyclopropoxy) pyridine-3-carbaldehyde (733 mg, 4.49 mmol, 1 eq) and ethyl 2-azidoacetate (1.74 g, 13.48 mmol, 1.89 mL, 3 eq) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -10 °C ~ 0 °C for 2 hr. TLC (Petroleum ether : Ethyl acetate = 5:1) indicated many new spots formed and compound 5 was also detected. The reaction was quenched with saturated NH_4Cl (60 mL), and then extracted with EtOAc (50 mL x 2). The combined organic layer was washed with brine (60 mL x 2), dried over Na_2SO_4, and then filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (SiO_2, 0-6% Ethyl acetate in petroleum ether). Compound ethyl (Z)-2-azido-3- [6-(cyclopropoxy)-3-pyridyl] prop-2-enoate (506 mg, crude) was obtained as a yellow oil.

LCMS (ESI) m/z: 275.1 $[M+H]^+$

Synthesis of ethyl 6-(cyclopropoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate

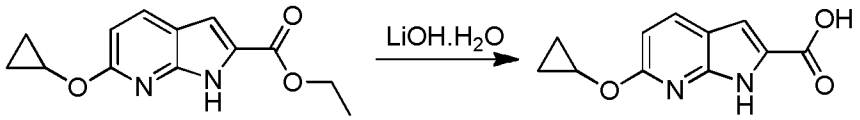


7 8

A solution of ethyl (Z)-2-azido-3-[6-(cyclopropoxy)-3-pyridyl]prop-2-enoate (500 mg, 1.82 mmol, 1 eq) in xylene (5 mL) was stirred at 140 °C for 30 min. LC-MS showed desired mass. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 0-25% Ethyl acetate in petroleum ether). Compound ethyl 6-(cyclopropoxy)-1H-pyrrolo [2,3-b]pyridine-2-carboxylate (396 mg, 1.45 mmol, 79.39% yield, 90% purity) was obtained as a colorless oil.

LCMS (ESI) m/z: 247.1 $[M+H]^+$; ^1H NMR was recorded.

Synthesis of 6-(cyclopropoxy)-1H-pyrrolo [2,3-b] pyridine-2-carboxylic acid

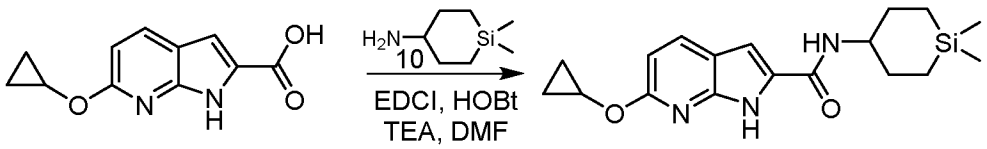


8 9

To a solution of ethyl 6-(cyclopropoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (340 mg, 1.38 mmol, 1 eq) in THF (1.5 mL) was added a solution of $LiOH.H_2O$ (347.62 mg, 8.28 mmol, 6 eq) in H_2O (1.5 mL). The mixture was stirred at 80 °C for 6 hr. TLC (Petroleum ether : Ethyl acetate=5:1) indicated compound 8 was consumed completely and one new spot formed. The reaction mixture was concentrated under reduced pressure to remove THF. The aqueous solution was adjusted to pH to 3-4 with aqueous HCl (1 N), and then filtered. The cake was washed with petroleum ether (15 mL), and then dried under reduced pressure. Compound 6-(cyclopropoxy)-1H-pyrrolo [2,3-b] pyridine-2-carboxylic acid (299 mg, 1.16 mmol, 84.36% yield, 85% purity) was obtained as a white solid.

^{1}H NMR (500MHz, DMSO-d_6) δ = 12.79 (br s, 1H), 12.29 - 11.95 (m, 1H), 8.02 - 7.91 (m, 1H), 7.07 - 6.99 (m, 1H), 6.61 (d, *J*=8.5 Hz, 1H), 4.28 (tt, *J*=3.1, 6.2 Hz, 1H), 0.81 - 0.66 (m, 4H).

Synthesis of 6-(cyclopropoxy) -N-(1,1-dimethylsilinan-4-yl) -1H-pyrrolo [2,3-b] pyridine-2-carboxamide



9 MPL-464

To a solution of 6-(cyclopropoxy)-1H-pyrrolo[2,3-b]pyridine-2-carboxylic acid (60 mg, 274.97 umol, 1 eq) and 1,1-dimethylsilinan-4-amine (59.31 mg, 329.96 umol, 1.2 eq, HCl salt) in DMF (2 mL) was added a solution of EDCI (158.14 mg, 824.90 umol, 3 eq) and HOBt (111.46 mg, 824.90 umol, 3 eq) in DMF (1 mL), followed by TEA (139.12 mg, 1.37 mmol, 191.36 uL, 5 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed desired mass. The reaction mixture was filtered. The filtrate was purified by prep-HPLC (column: Phenomenex Synergi C18

150*30mm*4um; mobile phase: A: 0.225% formic acid in water, B: CH_3CN; gradient: 60%-70%B over 11min). Compound 6-(cyclopropoxy) -N-(1,1-dimethylsilinan-4-yl) -1H-pyrrolo [2,3-b] pyridine-2-carboxamide (49.7 mg, 143.01 umol, 52.01% yield, 98.84% purity) was obtained as a white solid.

LCMS (ESI) m/z: 344.1 $[M+H]^+$; ^1H NMR (400MHz, DMSO-d6) δ = 11.88 (s, 1H), 8.00 - 7.90 (m, 2H), 7.01 (d, *J*=2.0 Hz, 1H), 6.58 (d, *J*=8.6 Hz, 1H), 4.30 - 4.19 (m, 1H), 3.70 (br d, *J*=7.8 Hz, 1H), 1.98 (br d, *J*=10.6 Hz, 2H), 1.66 - 1.49 (m, 2H), 0.83 - 0.54 (m, 8H), 0.11 - 0.01 (m, 6H).

Example 197: Biological Experiments

MIC (Minimum Inhibitory Concentration) determination of anti-tuberculosis drugs: The antituberculosis activity of each compound against M tb H37Rv was measured by the green fluorescent protein reporter assay (L. A. Collins, M. N. Torrero, S. G. Franzblau, *Antimicrob. Agents Chemother*. **1998**, *42*, 344-347). Briefly, the compound was initially dissolved in dimethylsulfoxide (DMSO), and two fold dilutions were made in DMSO. The same amount of each dilution of compound solution was added to 7H9 broth in microplates. The initial inoculum of 2 X 10^5 CFU/ml of Mtb H37Rv-GFP that was grown in Middlebrook 7H9 media was exposed to the compound for 10 days. The fluorescence was measured in a Fluostar Optima microplate fluorometer (BMG Labtech, Germany), and the MIC was defined as the lowest concentration of compounds that inhibited fluorescence by 90% comparing to the fluorescence of bacteria only wells. CFU = colony forming units.

The Table below shows anti-*Mycobacterium tuberculosis* activity of representative compounds of the invention:

Compound Number	M. TB H37Rv: MIC-MABA: MIC (µg/mL)		Compound Number	M. TB H37Rv: MIC-MABA: MIC (µg/mL)
MPL-001	0.03		MPL-122	3.1
MPL-002	0.056		MPL-124	3.1
MPL-003	0.01		MPL-125	3.1
MPL-006	0.3		MPL-126	3.1
MPL-007	0.12		MPL-127	0.54

Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)	Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)
MPL-008	0.051	MPL-128	2.3
MPL-008	0.017	MPL-129	0.5
MPL-012	0.048	MPL-130A	2.7
MPL-013	1.2	MPL-134	3.1
MPL-014	5.4	MPL-135	1.5
MPL-015	0.044	MPL-138	2.9
MPL-016	0.38	MPL-139	0.24
MPL-017	0.72	MPL-140	1.3
MPL-019	9	MPL-141	0.29
MPL-023	11	MPL-157	2.6
MPL-027	0.61	MPL-160	0.77
MPL-031	0.25	MPL-163	0.64
MPL-033	0.038	MPL-164	0.35
MPL-034	0.25	MPL-166	0.39
MPL-035	0.14	MPL-169	0.13
MPL-036	0.08	MPL-170	0.1
MPL-037	0.014	MPL-174	0.19
MPL-038	6.2	MPL-189	0.095
MPL-039	0.39	MPL-190	0.24
MPL-040	6.2	MPL-191	0.0087
MPL-041	8.5	MPL-192	0.0093
MPL-043	0.14	MPL-195	0.014
MPL-043	0.17	MPL-196	0.0048
MPL-044	0.013	MPL-197	0.013
MPL-045	0.069	MPL-199, MPL-213	0.046
MPL-062	0.19	MPL-200	0.072
MPL-063	0.14	MPL-202	0.11
MPL-064	0.16	MPL-207	0.0045
MPL-065a	0.013	MPL-208	0.0045
MPL-066	0.012	MPL-209	0.03
MPL-067	0.01	MPL-210	0.058
MPL-068	0.046	MPL-215	1.4
MPL-069	0.0099	MPL-216	0.041
MPL-070	0.49	MPL-218	0.037
MPL-071	0.049	MPL-219	0.9
MPL-092	1.2	MPL-221	0.2
MPL-093	1.1	MPL-222	0.19
MPL-094	0.049	MPL-226	0.75
MPL-095	1.5	MPL-229	0.0058
MPL-096	0.47	MPL-230	0.004

Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)	Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)
MPL-097	0.16	MPL-236	0.18
MPL-100	0.24	MPL-237	0.047
MPL-106	0.16	MPL-239	0.0078
MPL-108	0.02	MPL-253	0.056
MPL-109	0.022	MPL-254	0.2
MPL-110	0.022	MPL-259	0.054
MPL-111	0.0095	MPL-260	0.0075
MPL-118	0.017		
MPL-119	0.14		
MPL-232	0.03	MPL-351	0.248
MPL-274	0.01	MPL-352	0.122
MPL-275	0.031	MPL-353	0.124
MPL-276	0.015	MPL-366	0.492
MPL-277	0.045	MPL-367	0.988
MPL-280	0.043	MPL-368	0.49
MPL-281	0.0151	MPL-376	0.188
MPL-282	<0.004	MPL-379	0.332
MPL-282A	0.051	MPL-382	0.368
MPL-282B	0.197	MPL-387	0.163
MPL-284	0.026	MPL-388	0.012
MPL-285	0.016	MPL-389	0.216
MPL-290	0.005	MPL-391	0.051
MPL-292	0.0271	MPL-392	0.464
MPL-294	> 1.00	MPL-401	0.016
MPL-295	0.024	MPL-401A	0.319
MPL-295A	0.22	MPL-401B	0.007
MPL-295B	<0.004	MPL-402	0.962
MPL-301	0.015	MPL-434	0.061
MPL-305	0.015	MPL-435	1.0
MPL-316	0.015	MPL-445	0.119
MPL-316A	0.014	MPL-451	0.99
MPL-316B	0.25	MPL-452	0.118
MPL-318	0.134	MPL-453	0.284
MPL-319	0.499	MPL-454	0.458
MPL-320	0.25	MPL-455	0.121
MPL-321	0.519	MPL-464	0.124
MPL-322	0.484	MPL-465	0.008
MPL-328	0.061	MPL-466	0.119
MPL-329	0.491	MPL-466A	0.042
MPL-345	0.498	MPL-466B	> 1
MPL-346	0.464	MPL-467	0.121

Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)		Compound Number	M. TB H37Rv: MIC-MABA: MIC (μg/mL)
MPL-348	0.435		MPL-468	0.023
MPL-349	0.068		MPL-469	0.206
MPL-350	0.247		MPL-471	0.069

The Table below shows anti-*mycobacterium abscessus* activity of representative compounds of the invention:

Compound Number	Mab_ATCC:MIC MHII: MIC (μg/mL)		Compound Number	Mab_ATCC:MIC MHII: MIC (μg/mL)
MPL-012	4		MPL-135	8
MPL-034	2		MPL-188	8
MPL-044	2		MPL-195	2
MPL-045	2		MPL-200	16
MPL-067	0.25		MPL-208	1
MPL-118	1		MPL-209	1
MPL-119	0.5		MPL-229	0.12
MPL-124	16		MPL-230	16
MPL-127	8		MPL-239	16
MPL-232	0.38		MPL-401	0.75
MPL-274	0.75		MPL-464	1
MPL-295	0.28		MPL-466A	0.25
MPL-295B	0.12		MPL-466B	8
MPL-316	0.16		MPL-468	0.12
MPL-316A	0.19		MPL-471	1
MPL-387	0.5		MPL-453	0.5

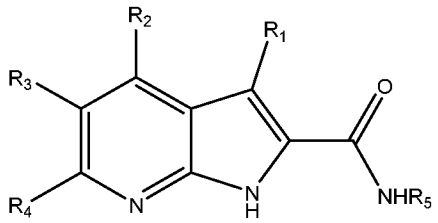
Key for Tables: MIC: Minimum Inhibitory Concentration; MABA: microplate-based Alamar Blue assay; Mab: *Mycobacterium abscessus*; ATCC: American Type Culture Collection; and MHII: Mueller-Hinton broth.

* * *

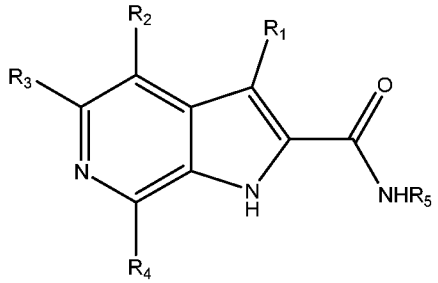
It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

The invention will be further described, without limitation, by the following numbered paragraphs:

1. A compound of Formula (I) or Formula (II):



(I)



(II)

wherein:

R_1 is hydrogen or lower alkyl;

R_2 is hydrogen, lower alkyl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

R_3 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

R_4 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, cycloalkoxy, or carboxamide;

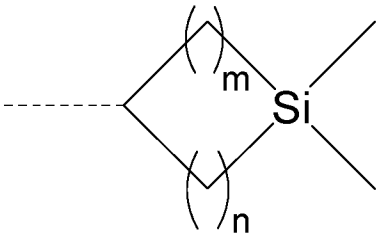
R_5 is:

(i) lower alkyl;

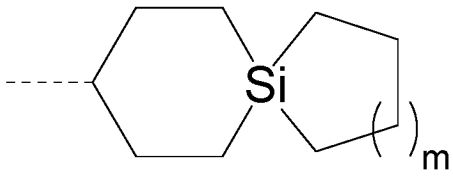
(ii) cycloalkyl, cycloalkylene or -CH_2-cycloalkyl;

(iii) spiral(C_8-C_{11})cycloalkyl;

(iv) phenyl;

(v) 

wherein m is 1, 2 or 3 and n is 1, 2, 3, or 4;

(vi) 

wherein m is 1 or 2;or

(vii) bridged cycloalkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound according to paragraph 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen or methyl.

3. The compound according to paragraph 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R_2 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

4. The compound according to any one of paragraphs 1-3, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

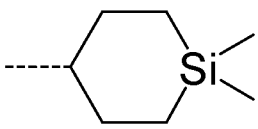
5. The compound according to any one of paragraphs 1-4, or a pharmaceutically acceptable salt thereof, wherein R_4 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

6. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is lower alkyl, optionally substituted with phenyl, said phenyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxy lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl;

7. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is cycloalkyl, cycloalkylene or -CH_2-cycloalkyl, said cycloalkyl, cycloalkylene or -CH_2-cycloalkyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy- lower alkyl, ethynyl, cyano, halo, or hydroxyl.

8. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is spiral(C_8-C_{11})cycloalkyl, optionally substituted with one or two substituents selected from lower alkyl and halogen.

9. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is



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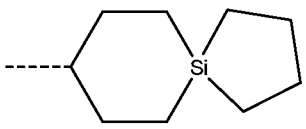

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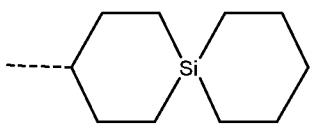

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10. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is (C_4-C_7)alkyl; (C_5-C_{10})cycloalkyl, -CH_2-(C_5-C_7)cycloalkyl, spiro(C_8-C_{11})cycloalkyl, or phenyl.

11. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is

(i) a bridged cycloalkyl substituted with one to four substituents selected from lower alkyl and hydroxyl;

(ii) (C_4-C_6)alkyl substituted with one or two substituents each independently selected from (C_1-C_4)alkyl, fluoro substituted (C_1-C_4)alkyl, methoxy, hydroxy(C_1-C_4)alkyl, methoxy(C_1-C_4)alkyl, ethynyl, cyano, halo, hydroxy and hydroxyl;

(iii) (C_5-C_9)cycloalkyl substituted with one to two substituents each independently selected from (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl, methoxy, and hydroxyl;

(iv) -CH_2-(C_5-C_7)cycloalkyl wherein the (C_5-C_7)cycloalkyl is substituted with one to two substituents each independently selected from (C_1-C_4)alkyl, fluoro-substituted (C_1-C_4)alkyl, methoxy and hydroxyl;

(v) spiro(C_8-C_{11})cycloalkyl substituted with one or two substituents indendently selected from lower alkyl and halogen;

(vi) phenyl substituted with one to two substituents each independently selected from (C_1-C_4)alkyl, fluoro substituted (C_1-C_4)alkyl, methoxy, hydroxy(C_1-C_4)alkyl, methoxy(C_1-C_4)alkyl, ethynyl, cyano, halo, or hydroxyl; or

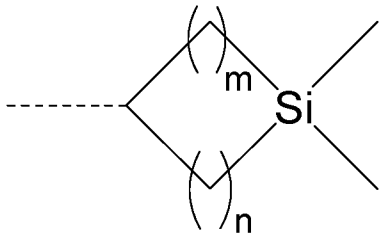
(vii) lower alkyl, substituted with phenyl, said phenyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxy lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl;

(viii) cycloalkyl, cycloalkylene or -CH_2-cycloalkyl, said cycloalkyl, cycloalkylene or -CH_2-cycloalkyl substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy- lower alkyl, ethynyl, cyano, halo, or hydroxyl;

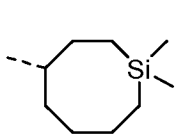
(ix) spiral(C_8-C_{11})cycloalkyl, substituted with one or two substituents independently selected from lower alkyl and halogen; or

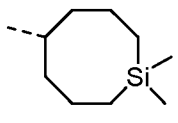
(x) phenyl, substituted with one or two substituents each independently selected from lower alkyl, fluoro-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl.

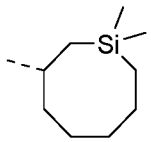
12. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, where R_5 is



wherein m is 1, 2 or 3 and n is 1, 2, 3, or 4.

13. The compound according to paragraph 12, or a pharmaceutically acceptable salt thereof, wherein R_5 is 

, 

, or 

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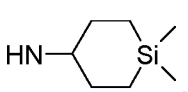
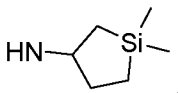
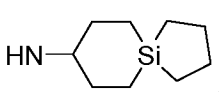
14. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is a bridged cycloalkyl.

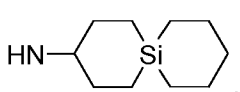
15. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_5 is a bridged cycloalkyl substituted with one to four substituents selected from lower alkyl and hydroxyl.

16. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_3NH is



, 

, 

, 

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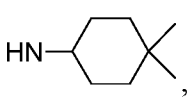
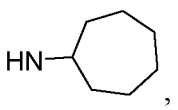
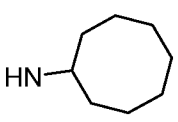
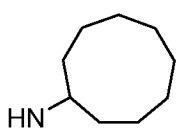


, 

, 

, or 

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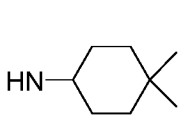
17. The compound according to any one of paragraphs 1-5, or a pharmaceutically acceptable salt thereof, wherein R_3NH is



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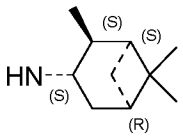

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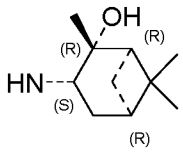

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18. The compound according to any one of paragraphs 1-17, or a pharmaceutically acceptable salt thereof, which has Formula (I).

19. The compound according to any one of paragraphs 1-17, or a pharmaceutically acceptable salt thereof, which has Formula (II) .

20. The compound of paragraph 1, or a pharmaceutically acceptable salt thereof, which is:
4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;
4-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-cyclopropyl-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyclopropyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-methyl-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
N-cyclooctyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-(trifluoromethyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-cyano-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4,6-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

5-chloro-4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohexyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-car boxamide;
5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5,7-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5,7-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
4-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H -pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohex-2-en-1-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
N-(3-bicyclo[3.2.1]octanyl)-4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-(trifluoro methyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-6- methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-[(1R, 2R, 3S, 5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-Pyrrolo[2,3-c]pyridine-2-carboxamide;

N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine -2-carboxamide;
N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo[2, 3-b] pyridine-2-carboxamide;
4-chloro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]Pyridine -2-carboxamide;
4-bromo-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
4-(methylamino)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H -pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-bromo-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

4-chloro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-6-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-cyclooctyl-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5,6-dimethyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- yrrolo[2,3-c]pyridine-2-carboxamide;
4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b] pyridine-2- carboxamide;
N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

5-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methoxy-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
7-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo [2,3-c]pyridine-2-carboxamide;
5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-fluoro-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo [2,3-c]pyridine-5-carboxylic acid;
2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid;
N2-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2,5-dicarboxamide;
N2-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-c]pyridine-2,5-dicarboxamide;
5-fluoro-7-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-fluoro-7-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
5-chloro-4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H– pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(2,2-difluorospiro[2.5]octan-6-yl)-4-fluoro-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4-bicyclo[2.2.2]octanyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-difluorospiro[2.5]octan-6-yl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;

4-chloro-N- (4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohex-2-en-1-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4-bicyclo[2.2.2]octanyl)-4-chloro-1H-pyrrolo[2,3-c] pyri-dine-2-carboxamide;
4-fluoro-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl] -1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-6-oxido-N-[(1S,2S,3S,5R)-2,6,6- trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-c]pyridin-6-ium-2-carboxamide;
4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-car-boxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide;
4-fluoro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-indole-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3 -yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbox amide;
4-fluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine -2-carboxamide;

4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b]pyridine-2-carboxamide;
4-chloro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2–carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilepan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-fluoro-3,6-dimethyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-fluoro-3,6-dimethyl-N-(6-silaspiro[5.5]undecan-3-yl)- 1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-cyclooctyl-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]- 6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilolan-3-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;

N-[(3R)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-[(3S)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilocan-5-yl)-4,5-difluoro-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-5-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-5-ylidene)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(4R)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(4S)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1 -dimethylsilinan-4-yl) -6-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1, 1-dimethylsilinan-4-yl)-5-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
4-chloro-N-(1,1-dimethylsilolan-3-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-[(3R)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(3S)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
5-(2-fluorophenyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-(3-pyridyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl) -6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
6-methoxy-N-(5-silaspiro [4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
6-methoxy-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
(S)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

(R)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
6-(cyclobutoxy)-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilocan-5-yl)-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5,6-dimethyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-5-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-5-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
5-chloro-4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilepan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-5-(trifluoromethyl)- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-I sopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

N-(1,1-dimethylsilolan-3-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1, 1-dimethylsilepan-4-yl) -4-methyl-5-(trifluoromethyl) -1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(1,1 -dimethylsilinan-4-yl) -5-methoxy-4- (trifluoromethyl) -1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo [2,3-c]pyridine-2-carboxamide; or
6-(cyclopropoxy) -N-(1,1-dimethylsilinan-4-yl) -1H-pyrrolo [2,3-b]pyridine-2-carboxamide.

21. A pharmaceutical composition, comprising a compound of any one of paragraphs 1-20, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or additives.

22. The pharmaceutical composition according to paragraph 21, further comprising one or more additional anti-infective agents.

23. The pharmaceutical composition according to paragraph 22, wherein said additional anti-infective agent is rifampicin, rifabutin, rifapentene, isoniazid, ethambutol, kanamycin, amikacin, capreomycin, clofazimine, cycloserine, para-aminosalicylic acid, linezolid, sutezolid, bedaquiline, delamanid, pretomanid, moxifloxacin or levofloxacin, or combinations thereof.

24. A method of treating a mycobacterial infection, comprising the step of administering a therapeutically effective amount of a compound of any one of paragraphs 1-20, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

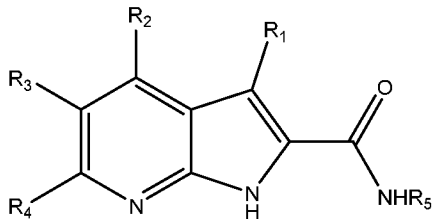
25. The method of paragraph 24, wherein the mycobacterial infection is caused by Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium kansasii, Mycobacterium abscessus or Mycobacterium chelonae.

26. The method of paragraph 24, wherein the mycobacterial infection is caused by *Mycobacterium tuberculosis*.

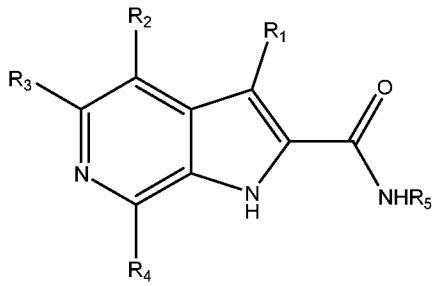
It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I) or Formula (II):



(I)



(II)

wherein:

R_1 is hydrogen or lower alkyl;

R_2 is hydrogen, lower alkyl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

R_3 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, or carboxamide;

R_4 is hydrogen, lower alkyl, aryl, heteroaryl, halo, cyano, trifluoromethyl, halo-lower alkyl, di-halo-lower alkyl, alkoxy, cycloalkoxy, or carboxamide;

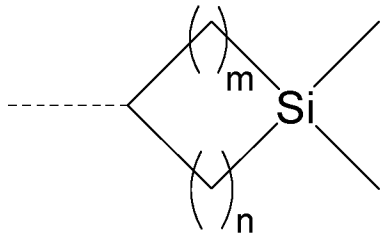
R_5 is:

(i) lower alkyl;

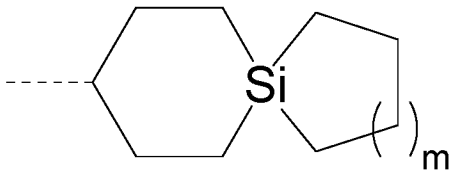
(ii) cycloalkyl;

(iii) spiral(C_8-C_{11})cycloalkyl;

(iv) phenyl;

(v) 

wherein m is 1, 2 or 3 and n is 1, 2, 3, or 4;

(vi) 

wherein m is 1 or 2;

or

(vii) a bridged cycloalkyl,

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen or methyl.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_2 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

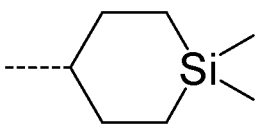
5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_4 is hydrogen, methyl, halo, cyano, trifluoromethyl, mono-fluoromethyl, di-fluoromethyl, methoxy, or carboxamide.

6. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is lower alkyl, optionally substituted with phenyl, said phenyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxy lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl.

7. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is cycloalkyl, cycloalkylene or -CH_2-cycloalkyl, said cycloalkyl, cycloalkylene or -CH_2-cycloalkyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl.

8. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is spiral(C_8-C_{11})cycloalkyl, optionally substituted with one or two substituents selected from lower alkyl and halogen.

9. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is



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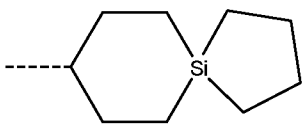
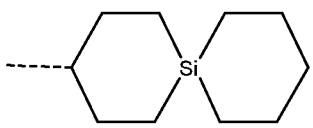


, or


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10. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is (C_4-C_7)alkyl; (C_5-C_{10})cycloalkyl, -CH_2-(C_5-C_7)cycloalkyl, spiro(C_8-C_{11})cycloalkyl, or phenyl.

11. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is

(i) a bridged cycloalkyl substituted with one to four substituents selected from lower alkyl and hydroxyl;

(ii) $(C_4\text{-}C_6)$alkyl substituted with one or two substituents each independently selected from $(C_1\text{-}C_4)$alkyl, fluoro substituted $(C_1\text{-}C_4)$alkyl, methoxy, hydroxy$(C_1\text{-}C_4)$alkyl, methoxy$(C_1\text{-}C_4)$alkyl, ethynyl, cyano, halo, hydroxy and hydroxyl;

(iii) $(C_5\text{-}C_9)$cycloalkyl substituted with one to two substituents each independently selected from $(C_1\text{-}C_4)$alkyl, fluoro-substituted $(C_1\text{-}C_4)$alkyl, methoxy, and hydroxyl;

(iv) $-CH_2\text{-}(C_5\text{-}C_7)$cycloalkyl wherein the $(C_5\text{-}C_7)$cycloalkyl is substituted with one to two substituents each independently selected from $(C_1\text{-}C_4)$alkyl, fluoro-substituted $(C_1\text{-}C_4)$alkyl, methoxy and hydroxyl;

(v) spiro$(C_8\text{-}C_{11})$cycloalkyl substituted with one or two substituents indendently selected from lower alkyl and halogen;

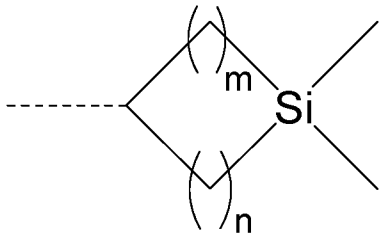
(vi) phenyl substituted with one to two substituents each independently selected from $(C_1\text{-}C_4)$alkyl, fluoro substituted $(C_1\text{-}C_4)$alkyl, methoxy, hydroxy$(C_1\text{-}C_4)$alkyl, methoxy$(C_1\text{-}C_4)$alkyl, ethynyl, cyano, halo, or hydroxyl;

(vii) lower alkyl, substituted with phenyl, said phenyl optionally substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxy lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl;

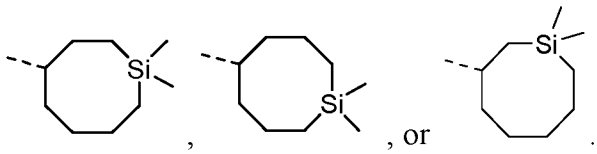
(viii) cycloalkyl, cycloalkylene or $-CH_2$-cycloalkyl, said cycloalkyl, cycloalkylene or $-CH_2$-cycloalkyl substituted with one or two substituents each independently selected from lower alkyl, halo-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy- lower alkyl, ethynyl, cyano, halo, or hydroxyl; or

(ix) phenyl, substituted with one or two substituents each independently selected from lower alkyl, fluoro-substituted lower alkyl, alkoxy, hydroxyl lower alkyl, alkoxy lower alkyl, ethynyl, cyano, halo, or hydroxyl.

12. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, where R_5 is



wherein m is 1, 2 or 3 and n is 1, 2, 3, or 4.

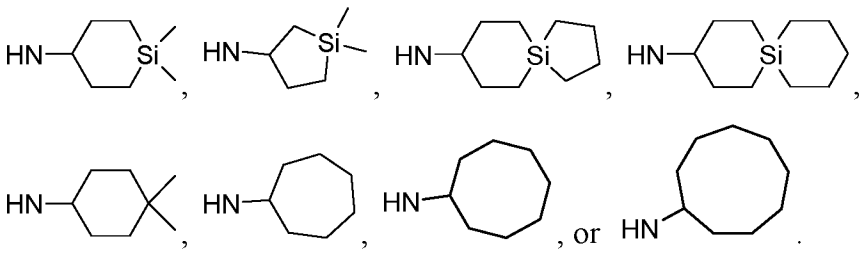
13. The compound according to paragraph 12, or a pharmaceutically acceptable salt thereof, wherein R_5 is 

, , or .

14. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is a bridged cycloalkyl.

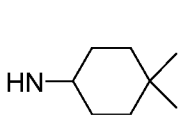
15. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_5 is a bridged cycloalkyl substituted with one to four substituents selected from lower alkyl and hydroxyl.

16. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_3NH is



, , , , , , , or .

17. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R_3NH is



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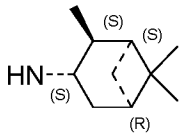
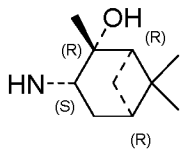


, or



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18. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which has Formula (I).

19. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which has Formula (II) .

20. The compound of claim 1, or a pharmaceutically acceptable salt thereof, which is:

4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;

4-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;

4-cyclopropyl-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-(4,4-dimethylcyclohexyl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

4-cyclopropyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

4-methyl-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;

N-cyclooctyl-4-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-(4,4-dimethylcyclohexyl)-4-(trifluoromethyl)-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;

4-cyano-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;

4,6-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;

4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-cyclooctyl-4-(trifluoromethyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-cyclooctyl-4-cyclopropyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

N-cyclooctyl-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

5-chloro-4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohexyl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-car boxamide;
5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5,7-dimethyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5,7-dimethyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
4-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H -pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohex-2-en-1-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
N-(3-bicyclo[3.2.1]octanyl)-4-chloro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-(trifluoro methyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-6- methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-[(1R, 2R, 3S, 5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-1H-Pyrrolo[2,3-c]pyridine-2-carboxamide;

N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3-methyl-1H-pyrrolo[2,3-c]pyridine -2-carboxamide;
N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo[2, 3-b] pyridine-2-carboxamide;
4-chloro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-spiro[3.5]nonan-7-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]Pyridine -2-carboxamide;
4-bromo-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-bromo-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
4-(methylamino)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H -pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-(4-methylcyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-bromo-N-cyclooctyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-(methylamino)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

4-chloro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4,5-difluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-6-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-cyclooctyl-6-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5,6-dimethyl-N-((1S,2S,3S,5R)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-1H- pyrrolo[2,3-b]pyridine-2-carboxamide;
N-cyclooctyl-5,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- yrrolo[2,3-c]pyridine-2-carboxamide;
4-cyano-N-cyclooctyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-cyano-N-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-(trifluoromethyl)-1H-pyrrolo[2,3-b] pyridine-2- carboxamide;
N-cyclooctyl-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

5-methoxy-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo [2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methoxy-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
7-fluoro-5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo [2,3-c]pyridine-2-carboxamide;
5-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-fluoro-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;
2-[[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]carbamoyl]-1H-pyrrolo [2,3-c]pyridine-5-carboxylic acid;
2-[(4,4-dimethylcyclohexyl)carbamoyl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid;
N2-(4,4-dimethylcyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2,5-dicarboxamide;
N2-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-c]pyridine-2,5-dicarboxamide;
5-fluoro-7-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyr-rolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-fluoro-7-methyl-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
5-chloro-4-fluoro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H– pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(2,2-difluorospiro[2.5]octan-6-yl)-4-fluoro-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4-bicyclo[2.2.2]octanyl)-4-fluoro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-spiro[2.5]octan-6-yl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-difluorospiro[2.5]octan-6-yl)-1H-pyrrolo[2,3-c]pyridine-2- carboxamide;

4-chloro-N- (4-fluoro-4-methyl-cyclohexyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(4,4-dimethylcyclohex-2-en-1-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(4-bicyclo[2.2.2]octanyl)-4-chloro-1H-pyrrolo[2,3-c] pyri-dine-2-carboxamide;
4-fluoro-3-methyl-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl] -1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-6-oxido-N-[(1S,2S,3S,5R)-2,6,6- trimethyl-norpinan-3-yl]-1H-pyrrolo[2,3-c]pyridin-6-ium-2-carboxamide;
4-fluoro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-car-boxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo [2,3-c]pyridine-2-carboxamide;
4-fluoro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-6-methyl-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-fluoro-4-methoxy-1H-indole-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-cyano-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3 -yl]-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(4,4-dimethylcyclohexyl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-fluoro-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-7-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carbox amide;
4-fluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b]pyridine -2-carboxamide;

4-(trifluoromethyl)-N-[(1S,2S,3S,5R)-2,6,6-trimethylnorpinan-3-yl]-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-(trifluoromethyl)-N-(1,7,7-trimethylnorbornan-2-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
N-(1, 1-dimethylsilinan-4-yl)-4, 5-difluoro-6-methyl-1H-pyrrolo [2, 3-b]pyridine-2-carboxamide;
4-chloro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2–carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,6-dimethyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-4-fluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan -3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilepan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-4-yl)-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-fluoro-3,6-dimethyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-fluoro-3,6-dimethyl-N-(6-silaspiro[5.5]undecan-3-yl)- 1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4,5-difluoro-6-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-cyclooctyl-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4,5-difluoro-N-[(1R,2R,3S,5R)-2-hydroxy-2,6,6-trimethyl-norpinan-3-yl]- 6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilolan-3-yl)-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;

N-[(3R)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-[(3S)-1,1-dimethylsilolan-3-yl]-4,5-difluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilocan-5-yl)-4,5-difluoro-6-methyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-5-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilocan-5-ylidene)-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(4R)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-chloro-N-[(4S)-1,1-dimethylsilepan-4-yl]-4-fluoro-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1 -dimethylsilinan-4-yl) -6-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-6-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1, 1-dimethylsilinan-4-yl)-5-methoxy-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-(3-pyridyl)-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
4-chloro-N-(1,1-dimethylsilolan-3-yl)-6-methyl-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
4-chloro-N-[(3R)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-[(3S)-1,1-dimethylsilolan-3-yl]-6-methyl-1H-pyrrolo [2,3-b] pyridine-2-carboxamide;
5-(2-fluorophenyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
5-(3-pyridyl)-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(4,4-dimethylcyclohexyl) -6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
6-methoxy-N-(5-silaspiro [4.5]decan-8-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
6-methoxy-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2- carboxamide;
(S)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;

(R)-N-(1,1-dimethylsilepan-4-yl)-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
6-(cyclobutoxy)-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-6-methoxy-1H-pyrrolo[2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilocan-5-yl)-6-methoxy-1H-pyrrolo[2,3-b] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5,6-dimethyl-1H-pyrrolo [2,3-b]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine- 2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-5-methyl-N-(5-silaspiro[4.5]decan-8-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-5-methyl-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-chloro-N-(1,1-dimethylsilinan-4-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilinan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
5-chloro-N-(1,1-dimethylsilepan-4-yl)-4-fluoro-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
5-chloro-4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilinan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4,5-dichloro-N-(1,1-dimethylsilepan-4-yl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-5-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(5-silaspiro[4.5]decan-8-yl)-5-(trifluoromethyl)-1H- pyrrolo[2,3-c]pyridine-2-carboxamide;
4-fluoro-N-(6-silaspiro[5.5]undecan-3-yl)-5-(trifluoromethyl)- 1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methyl-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-methoxy-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-I sopropoxy-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;

N-(1,1-dimethylsilolan-3-yl)-5-(trifluoromethyl)-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-5-phenyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1, 1-dimethylsilepan-4-yl) -4-methyl-5-(trifluoromethyl) -1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(1,1 -dimethylsilinan-4-yl) -5-methoxy-4- (trifluoromethyl) -1H-pyrrolo[2,3-c] pyridine-2-carboxamide;
N-(1,1-dimethylsilinan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide;
N-(1,1-dimethylsilepan-4-yl)-4-fluoro-3,5-dimethyl-1H-pyrrolo [2,3-c]pyridine-2-carboxamide;
or 6-(cyclopropoxy) -N-(1,1-dimethylsilinan-4-yl) -1H-pyrrolo [2,3-b]pyridine-2-carboxamide.

21. A pharmaceutical composition, comprising a compound of claim 1, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or additives.

22. The pharmaceutical composition according to claim 21, further comprising one or more additional anti-infective agents.

23. The pharmaceutical composition according to claim 21, wherein said additional anti-infective agent is rifampicin, rifabutin, rifapentene, isoniazid, ethambutol, kanamycin, amikacin, capreomycin, clofazimine, cycloserine, para-aminosalicylic acid, linezolid, sutezolid, bedaquiline, delamanid, pretomanid, moxifloxacin or levofloxacin, or combinations thereof.

24. A method of treating a mycobacterial infection, comprising the step of administering a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

25. The method of claim 24, wherein the mycobacterial infection is caused by Mycobacterium tuberculosis, Mycobacterium avium, Mycobacterium kansasii, Mycobacterium abscessus or Mycobacterium chelonae.

26. The method of claim 24, wherein the mycobacterial infection is caused by *Mycobacterium tuberculosis*.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/052934

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 10, 18, 21-23

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/052934

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/416; A61K 31/475; C07D 403/12; C07D 405/14 (2020.01)
CPC - A61K 31/416; A61K 31/475; C07D 403/12; C07D 405/14 (2020.08)

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)
see Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2017/0107178 A1 (IOMET PHARMA LTD) 20 April 2017 (20.04.2017) entire document	1-6, 10, 18, 21-23
A	US 2011/0136807 A1 (HANGAUER JR) 09 June 2011 (09.06.2011) entire document	1-6, 10, 18, 21-23
A	US 9,345,247 B2 (BAYER CROPSCIENCE AG) 24 May 2016 (24.05.2016) entire document	1-6, 10, 18, 21-23

☐ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 December 2020	02 FEB 2021
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/052934

Continued from Box No. III Observations where unity of invention is lacking

The first invention of Group I+ is restricted to a compound of Formula (I): wherein: R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is lower alkyl, wherein the lower alkyl is unsubstituted C4 alkyl; or a pharmaceutically acceptable salt thereof; and pharmaceutical compositions thereof.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-23 are drawn to compounds of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and pharmaceutical compositions thereof.

Group II+: claims 24-26 are drawn to methods of treating a mycobacterial infection thereof.

The first invention of Group I+ is restricted to a compound of Formula (I): wherein: R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is lower alkyl, wherein the lower alkyl is unsubstituted C4 alkyl; or a pharmaceutically acceptable salt thereof; and pharmaceutical compositions thereof. It is believed that claims 1-6, 10, 18, and 21-23 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

The first invention of Group II+ is restricted to a method of treating a mycobacterial infection, comprising the step of administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, wherein the compound is a compound of Formula (I): wherein: R1 is hydrogen; R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; R5 is lower alkyl, wherein the lower alkyl is unsubstituted C4 alkyl; or a pharmaceutically acceptable salt thereof.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of Formula (I): wherein: R1 is hydrogen; R2 is cyano; R3 is hydrogen; R4 is hydrogen; R5 is lower alkyl, wherein the lower alkyl is unsubstituted C4 alkyl; or a pharmaceutically acceptable salt thereof; pharmaceutical compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and pharmaceutical compositions thereof, are not present in Group II+, and the special technical features of Group II+, methods of treating a mycobacterial infection thereof, are not present in Group I+.

The Groups I+ and II+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables, R1, R2, R3, R4, R5 and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ and II+ were considered to share the technical features of a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof; a pharmaceutical composition, comprising a compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers and/or additives; a method of treating a mycobacterial infection, comprising the step of administering a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, to a patient in need thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 2017/0107178 A1 to IOmet Pharma Ltd.

US 2017/0107178 A1 to IOmet Pharma Ltd. teaches a compound of Formula (I): wherein: R1 is hydrogen; R2 is cyano; R3 is hydrogen; R4 is hydrogen; R5 is lower alkyl (Pg. 40, Compound 80); a pharmaceutical composition (Para. [0408], a pharmaceutical composition comprising a compound), comprising a compound (Para. [0408]), and one or more pharmaceutically acceptable carriers and/or additives (Para. [0408], the composition further comprises a pharmaceutically acceptable additive and/or excipient); a method of treating a mycobacterial infection (Claim 19; Para. [0405], When the disease is an infectious disease ... a bacterial infection), comprising the step of administering a therapeutically effective amount of a compound, to a patient in need thereof (Claim 19, administering an effective amount of a compound; Para. [0410], administering to a patient a compound or a composition).

The inventions listed in Groups I+ and II+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.