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(54) Title: AMINOPYRIDINE COMPOUNDS AND METHODS FOR THE PREPARATION AND USE THEREOF

(57) Abstract: The present invention relates generally to therapeutics targeting the bacterium *Porphyromonas gingivalis*, including its proteases arginine gingipain A/B (Rgp), and their use for the treatment of disorders associated with *P. gingivalis* infection, including brain disorders such as Alzheimer's disease. In certain embodiments, the invention provides compounds according to Formula I and Formula III, as described herein, and pharmaceutically acceptable salts thereof.

AMINOPYRIDINE COMPOUNDS AND METHODS FOR THE PREPARATION AND USE THEREOF

5 CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Pat. Appl. No. 62/504,442, filed on May 10, 2017, and U.S. Provisional Pat. Appl. No. 62/504,480, filed on May 10, 2017, which applications are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

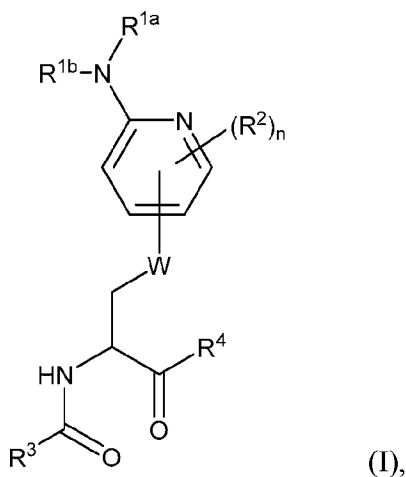
10 [0002] Infection with the bacterium *Porphyromonas gingivalis* has been linked to the development of periodontal disease, Alzheimer's disease and other brain disorders, cardiovascular disease, diabetes, cancer, liver disease, kidney disease, preterm birth, arthritis, pneumonia and other disorders. *P. gingivalis* is an anaerobic asaccharolytic gram-negative rod bacterium that is known to infect the oral cavity and translocate systemically into
15 coronary arteries, aorta, placental tissue, the brain, the kidneys, and the liver. The bacterium has also been identified in cancerous tissues and a mechanism has been proposed by which gingipains can trigger immortalization and metastasis. See: Gandhimadhi, *et al. Journal of Indian Society of Periodontology*, 2010;14(2):114-120; Liao, *et al., Med Hypotheses*, 2009. 72(6): 732-5; Byrne, *et al., Oral Microbiol Immunol*, 2009. 24(6): 469-77; Mahendra, *et al., J Maxillofac Oral Surg*, 2009. 8(2): 108-13; Stelzel, *et al., J Periodontol*, 2002. 73(8): 868-70; Katz, *et al., Journal of Dental Research*, 2009. 88(6): 575-578; Poole, *et al., J Alzheimers Dis*, 2015, 43(1): 67-80; Ishikawa, *et al., Biochim Biophys Acta*, 2013. 1832(12): 2035-2043; Inaba, *et al., Cellular Microbiology*, 2014. 16(1): 131-145.

25 [0003] *P. gingivalis* produces proteases called gingipains, including Arginine Gingipain A (RgpA), Arginine Gingipain B (RgpB) and Lysine Gingipain (Kgp). Gingipains contribute to many functions of the organism including its survival and virulence. Gingipains can be secreted, transported to outer membrane surfaces of *P. gingivalis*, or released in outer membrane vesicles by the bacterium. Gingipains degrade a broad range of proteins (*e.g.*, immunoglobulins, proteinase inhibitors, actin, and collagen) which can lead to cytoskeleton

collapse and apoptosis in many types of cells. Recent research has demonstrated that inhibitors of gingipains can prevent *P. gingivalis*-induced cell death. See: Travis, *et al.*, *Adv Exp Med Biol*, 2000. 477: 455-65; Sheets, *et al.*, *Infect Immun*, 2005. 73(3): 1543-52; Sheets, *et al.*, *Infect Immun*, 2006. 74(10): 5667-78; Stathopoulou, *et al.*, *BMC Microbiol*, 2009. 9: 107. New compounds for the inhibition of gingipain activity and the treatment of diseases associated with gingipain activity and *P. gingivalis* infection are needed. The present invention addresses this and other needs.

BRIEF SUMMARY OF THE INVENTION

[0004] In one embodiment, the invention provides a compound according to Formula I:



or a pharmaceutically acceptable salt thereof, wherein

W is selected from the group consisting of a bond, CH₂, and O;

R^{1a} and R^{1b} are independently selected from the group consisting of H and C₁₋₆ alkyl;

R² is selected from the group consisting of C₁₋₆ alkyl and halogen;

subscript n is 0 or 1;

R³ is selected from the group consisting of C₃₋₈ alkyl, C₃₋₈ cycloalkyl,

C₃₋₁₂ heterocyclyl, C₆₋₁₀ aryl, and C₅₋₁₂ heteroaryl wherein R³ is optionally substituted with one or more R^{3a} substituents;

each R^{3a} is independently selected from the group consisting of

halogen, -CN, -NO₂, -N₃, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy,

C₁₋₄ haloalkoxy, -N(R^c)₂, -(CH₂)_kC(O)R^b, -NR^c(CH₂)_uC(O)R^b,

-O(CH₂)_uC(O)R^b, -(CH₂)_kCONR^cR^c, -(CH₂)_kNR^cC(O)R^b,

-NR^c(CH₂)_uCONR^cR^c, -NR^c(CH₂)_uNR^cC-(O)R^b, -O(CH₂)_uCONR^cR^c,

and -O(CH₂)_uNR^cC(O)R^b, and optionally substituted triazolyl;

each R^b is independently selected from the group consisting of C_{1-4} alkyl,

C_{1-4} haloalkyl, and C_{1-4} deuterioalkyl;

each R^c is independently selected from the group consisting of hydrogen and

C_{1-8} alkyl;

5 each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6;

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6;

R^4 is selected from the group consisting of $-CH_2R^{4a}$ and C_{1-6} haloalkyl;

R^{4a} is selected from the group consisting of $-O-R^5$, $-S-R^6$, $-SO-R^6$, $-SO_2-R^6$, $-N(R^7)_2$,
and C_{5-12} heteroaryl;

10 R^5 is selected from the group consisting of phenyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and

C_{5-12} heteroaryl, wherein phenyl is substituted with 1-5 halogens, and wherein

C_{5-12} heteroaryl is optionally substituted with halogen or C_{1-3} haloalkyl;

R^6 is selected from the group consisting of phenyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and

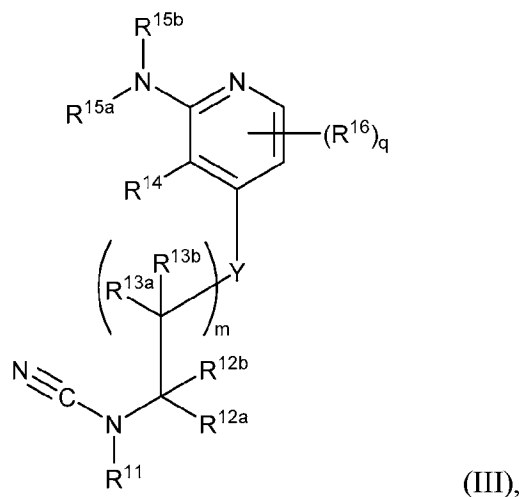
C_{5-12} heteroaryl, wherein phenyl is optionally substituted with 1-5 halogens,

15 and wherein C_{5-12} heteroaryl is optionally substituted with halogen or

C_{1-3} haloalkyl; and

each R^7 is independently selected C_{1-6} alkyl.

[0005] In one embodiment, the invention provides a compound according to Formula III:



20 or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is selected from C_{1-6} alkyl and C_{3-8} cycloalkyl;

R^{12a} and R^{12b} are independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, or

R^{12a} and R^{12b} are taken together to form C_{3-6} cycloalkyl, or

R^{12a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl which is optionally substituted with one or more R^{17} ;
each R^{13a} and each R^{13b} is independently selected from H, -OH, and C_{1-6} alkyl, or
one R^{13a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl,
5 or
one R^{13b} and R^{12b} are taken together to form a 5- or 6-membered ring;
 R^{14} is selected from H and halogen, or
 R^{14} , R^{12a} , and R^{12b} are taken together to form a 6- to 8-membered ring, which is optionally substituted with one or more R^{18} , or
10 R^{14} and one R^{13a} are taken together to form a 5- to 8-membered ring, which is optionally substituted with one or more R^{18} , or
 R^{14} is taken together with one R^{13a} and one R^{13b} on the same carbon atom to form a 5- to 8-membered ring, which is optionally substituted with one or more R^{18} , or
15 R^{14} , R^{11} , and R^{12a} are taken together to form a 6- to 10-membered bicyclic ring, which is optionally substituted with one or more R^{18} ;
 R^{15a} and R^{15b} are independently selected from H and C_{1-6} alkyl;
 R^{16} is independently selected from C_{1-6} alkyl and halogen;
each R^{17} is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl,
20 C_{1-6} haloalkoxy, -OH, and $-N(R^{17a})_2$, wherein each R^{17a} is independently selected from H and C_{1-6} alkyl;
each R^{18} is independently selected from C_{1-6} alkyl and halogen;
Y is selected from O, S, $C(R^{19a})_2$, and NR^{19b} ;
each R^{19a} is selected from H and C_{1-6} alkyl, or
25 one R^{19a} and one R^{13b} on adjacent atoms are taken together to form a double bond;
 R^{19b} is selected from H and C_{1-6} alkyl, or
 R^{19b} and R^{11} are taken together to form a 4- to 6-membered ring;
subscript m is 0, 1, 2, or 3; and
30 subscript q is 0 or 1.

[0006] In a related embodiment, the invention provides a pharmaceutical composition containing a compound as described herein, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

[0007] In another embodiment, the invention provides a method of inhibiting a gingipain. The method includes contacting the gingipain with an effective amount of a compound as described herein.

[0008] In another embodiment, the invention provides a method of treating a disease or condition associated with *P. gingivalis* infection. The method includes administering to a subject in need thereof an effective amount of a compound or pharmaceutical composition as described herein.

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0009] Inhibition of gingipains has been shown to protect cells, prevent bacterial growth, increase immune system surveillance of *P. gingivalis*, and protect against bacterial reinfection. The present invention provides potent nonpeptidic compounds for inhibition of arginine gingipains. The compounds can be used to prevent cell death, inflammation, and other pathology in a variety of diseases associated with *P. gingivalis* infection, including aging-related conditions such as Alzheimer's disease.

II. Definitions

[0010] As used herein, the term "alkyl," by itself or as part of another substituent, refers to a straight or branched, saturated, aliphatic radical having the number of carbon atoms indicated. Alkyl can include any number of carbons, such as C₁₋₂, C₁₋₃, C₁₋₄, C₁₋₅, C₁₋₆, C₁₋₇, C₁₋₈, C₁₋₉, C₁₋₁₀, C₂₋₃, C₂₋₄, C₂₋₅, C₂₋₆, C₃₋₄, C₃₋₅, C₃₋₆, C₄₋₅, C₄₋₆ and C₅₋₆. For example, C₁₋₆ alkyl includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, etc. Alkyl can also refer to alkyl groups having up to 20 carbons atoms, such as, but not limited to heptyl, octyl, nonyl, decyl, etc. Alkyl groups can be substituted or unsubstituted. For example, "substituted alkyl" groups can be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

[0011] As used herein, the term "alkoxy," by itself or as part of another substituent, refers to a group having the formula -OR, wherein R is alkyl.

[0012] As used herein, the term “cycloalkyl,” by itself or as part of another substituent, refers to a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing from 3 to 12 ring atoms, or the number of atoms indicated.

Cycloalkyl can include any number of carbons, such as C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈,

5 C₃₋₉, C₃₋₁₀, C₃₋₁₁, and C₃₋₁₂. Saturated monocyclic cycloalkyl rings include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cyclooctyl. Saturated bicyclic and polycyclic cycloalkyl rings include, for example, norbornane, [2.2.2] bicyclooctane, decahydronaphthalene and adamantane. Cycloalkyl groups can also be partially unsaturated, having one or more double or triple bonds in the ring. Representative cycloalkyl groups that
10 are partially unsaturated include, but are not limited to, cyclobutene, cyclopentene, cyclohexene, cyclohexadiene (1,3- and 1,4-isomers), cycloheptene, cycloheptadiene, cyclooctene, cyclooctadiene (1,3-, 1,4- and 1,5-isomers), norbornene, and norbornadiene.

When cycloalkyl is a saturated monocyclic C₃₋₈ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

15 When cycloalkyl is a saturated monocyclic C₃₋₆ cycloalkyl, exemplary groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Cycloalkyl groups can be substituted or unsubstituted. For example, “substituted cycloalkyl” groups can be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

20 [0013] As used herein, the term “alkylene” refers to an alkyl group, as defined above, linking at least two other groups (*i.e.*, a divalent alkyl radical). The two moieties linked to the alkylene group can be linked to the same carbon atom or different carbon atoms of the alkylene group.

[0014] As used herein, the term “alkylthio,” by itself or as part of another substituent,
25 refers to a group having the formula -SR, wherein R is alkyl.

[0015] As used herein, the term “heteroalkyl,” by itself or as part of another substituent, refers to an alkyl group of any suitable length and having from 1 to 3 heteroatoms such as N, O and S. For example, heteroalkyl can include ethers, thioethers and alkyl-amines.

Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The
30 heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -S(O)₂-. The heteroatom portion of the heteroalkyl can replace a hydrogen of the alkyl group to form a

hydroxy, thio, or amino group. Alternatively, the heteroatom portion can be the connecting atom, or be inserted between two carbon atoms.

[0016] As used herein, the terms “halo” and “halogen,” by themselves or as part of another substituent, refer to a fluorine, chlorine, bromine, or iodine atom.

5 **[0017]** As used herein, the term “haloalkyl,” by itself or as part of another substituent, refers to an alkyl group where some or all of the hydrogen atoms are replaced with halogen atoms. As for alkyl groups, haloalkyl groups can have any suitable number of carbon atoms, such as C₁₋₆. For example, haloalkyl includes trifluoromethyl, fluoromethyl, *etc.* In some instances, the term “perfluoro” can be used to define a compound or radical where all the
10 hydrogens are replaced with fluorine. For example, perfluoromethyl refers to 1,1,1-trifluoromethyl.

[0018] As used herein, the term “haloalkoxy,” by itself or as part of another substituent, refers to an alkoxy group where some or all of the hydrogen atoms are replaced with halogen atoms.

15 **[0019]** As used herein, the term “halocycloalkyl,” by itself or as part of another substituent, refers to a cycloalkyl group where some or all of the hydrogen atoms are replaced with halogen atoms.

[0020] As used herein, the term “deuteroalkyl,” by itself or as part of another substituent, refers to an alkyl group where some or all of the hydrogen atoms are replaced with deuterium
20 atoms. As for alkyl groups, deuteroalkyl groups can have any suitable number of carbon atoms, such as C₁₋₆. In some instances, the term “perdeutero” can be used to define a compound or radical where all the hydrogens are replaced with deuterium.

[0021] As used herein, the term “aryl,” by itself or as part of another substituent, refers to an aromatic ring system having any suitable number of carbon ring atoms and any suitable
25 number of rings. Aryl groups can include any suitable number of carbon ring atoms, such as C₆, C₇, C₈, C₉, C₁₀, C₁₁, C₁₂, C₁₃, C₁₄, C₁₅ or C₁₆, as well as C₆₋₁₀, C₆₋₁₂, or C₆₋₁₄. Aryl groups can be monocyclic, fused to form bicyclic (*e.g.*, benzocyclohexyl) or tricyclic groups, or linked by a bond to form a biaryl group. Representative aryl groups include phenyl, naphthyl and biphenyl. Other aryl groups include benzyl, having a methylene linking group. Some
30 aryl groups have from 6 to 12 ring members, such as phenyl, naphthyl or biphenyl. Other aryl groups have from 6 to 10 ring members, such as phenyl or naphthyl. Some other aryl

groups have 6 ring members, such as phenyl. Aryl groups can be substituted or unsubstituted. For example, “substituted aryl” groups can be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

- 5 **[0022]** As used herein, the term “heteroaryl,” by itself or as part of another substituent, refers to a monocyclic or fused bicyclic or tricyclic aromatic ring assembly containing 5 to 16 ring atoms, where from 1 to 5 of the ring atoms are a heteroatom such as N, O or S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -S(O)₂-.
- 10 Heteroaryl groups can include any number of ring atoms, such as C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, or C₃₋₁₂, wherein at least one of the carbon atoms is replaced by a heteroatom. Any suitable number of heteroatoms can be included in the heteroaryl groups, such as 1, 2, 3, 4; or 5, or 1 to 2, 1 to 3, 1 to 4, 1 to 5, 2 to 3, 2 to 4, 2 to 5, 3 to 4, or 3 to 5. For example, heteroaryl groups can be C₅₋₈ heteroaryl, wherein 1 to 4 carbon ring atoms are
- 15 replaced with heteroatoms; or C₅₋₈ heteroaryl, wherein 1 to 3 carbon ring atoms are replaced with heteroatoms; or C₅₋₆ heteroaryl, wherein 1 to 4 carbon ring atoms are replaced with heteroatoms; or C₅₋₆ heteroaryl, wherein 1 to 3 carbon ring atoms are replaced with heteroatoms. The heteroaryl group can include groups such as pyrrole, pyridine, imidazole, pyrazole, triazole, tetrazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and
- 20 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. The heteroaryl groups can also be fused to aromatic ring systems, such as a phenyl ring, to form members including, but not limited to, benzopyrroles such as indole and isoindole, benzopyridines such as quinoline and isoquinoline, benzopyrazine (quinoxaline), benzopyrimidine (quinazoline), benzopyridazines such as phthalazine and cinnoline, benzothiophene, and benzofuran. Other
- 25 heteroaryl groups include heteroaryl rings linked by a bond, such as bipyridine. Heteroaryl groups can be substituted or unsubstituted. For example, “substituted heteroaryl” groups can be substituted with one or more groups selected from halo, hydroxy, amino, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

- [0023]** The heteroaryl groups can be linked via any position on the ring. For example,
- 30 pyrrole includes 1-, 2- and 3-pyrrole, pyridine includes 2-, 3- and 4-pyridine, imidazole includes 1-, 2-, 4- and 5-imidazole, pyrazole includes 1-, 3-, 4- and 5-pyrazole, triazole includes 1-, 4- and 5-triazole, tetrazole includes 1- and 5-tetrazole, pyrimidine includes 2-, 4-, 5- and 6- pyrimidine, pyridazine includes 3- and 4-pyridazine, 1,2,3-triazine includes 4- and

5-triazine, 1,2,4-triazine includes 3-, 5- and 6-triazine, 1,3,5-triazine includes 2-triazine, thiophene includes 2- and 3-thiophene, furan includes 2- and 3-furan, thiazole includes 2-, 4- and 5-thiazole, isothiazole includes 3-, 4- and 5-isothiazole, oxazole includes 2-, 4- and 5-oxazole, isoxazole includes 3-, 4- and 5-isoxazole, indole includes 1-, 2- and 3-indole, 5 isoindole includes 1- and 2-isoindole, quinoline includes 2-, 3- and 4-quinoline, isoquinoline includes 1-, 3- and 4-isoquinoline, quinazoline includes 2- and 4-quinazoline, cinnoline includes 3- and 4-cinnoline, benzothiophene includes 2- and 3-benzothiophene, and benzofuran includes 2- and 3-benzofuran.

[0024] Some heteroaryl groups include those having from 5 to 10 ring members and from 1 10 to 3 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, isoxazole, indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, and benzofuran. Other heteroaryl groups include those having from 5 to 8 ring members and from 1 to 3 15 heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole. Some other heteroaryl groups include those having from 9 to 12 ring members and from 1 to 3 heteroatoms, such as indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline, benzothiophene, benzofuran and bipyridine. 20 Still other heteroaryl groups include those having from 5 to 6 ring members and from 1 to 2 ring atoms including N, O or S, such as pyrrole, pyridine, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, thiophene, furan, thiazole, isothiazole, oxazole, and isoxazole.

[0025] Some heteroaryl groups include from 5 to 10 ring members and only nitrogen heteroatoms, such as pyrrole, pyridine, imidazole, pyrazole, triazole, pyrazine, pyrimidine, 25 pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), indole, isoindole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, and cinnoline. Other heteroaryl groups include from 5 to 10 ring members and only oxygen heteroatoms, such as furan and benzofuran. Some other heteroaryl groups include from 5 to 10 ring members and only sulfur heteroatoms, such as thiophene and benzothiophene. Still other heteroaryl groups include 30 from 5 to 10 ring members and at least two heteroatoms, such as imidazole, pyrazole, triazole, pyrazine, pyrimidine, pyridazine, triazine (1,2,3-, 1,2,4- and 1,3,5-isomers), thiazole, isothiazole, oxazole, isoxazole, quinoxaline, quinazoline, phthalazine, and cinnoline.

[0026] As used herein, the term “heterocyclyl,” by itself or as part of another substituent, refers to a saturated ring system having from 3 to 12 ring members and from 1 to 4 heteroatoms of N, O and S. Additional heteroatoms can also be useful, including, but not limited to, B, Al, Si and P. The heteroatoms can be oxidized to form moieties such as, but not limited to, -S(O)- and -S(O)₂-. Heterocyclyl groups can include any number of ring atoms, such as, C₃₋₆, C₄₋₆, C₅₋₆, C₃₋₈, C₄₋₈, C₅₋₈, C₆₋₈, C₃₋₉, C₃₋₁₀, C₃₋₁₁, or C₃₋₁₂, wherein at least one of the carbon atoms is replaced by a heteroatom. Any suitable number of carbon ring atoms can be replaced with heteroatoms in the heterocyclyl groups, such as 1, 2, 3, or 4, or 1 to 2, 1 to 3, 1 to 4, 2 to 3, 2 to 4, or 3 to 4. The heterocyclyl group can include groups such as aziridine, azetidine, pyrrolidine, piperidine, azepane, azocane, quinuclidine, pyrazolidine, imidazolidine, piperazine (1,2-, 1,3- and 1,4-isomers), oxirane, oxetane, tetrahydrofuran, oxane (tetrahydropyran), oxepane, thiirane, thietane, thiolane (tetrahydrothiophene), thiane (tetrahydrothiopyran), oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, dioxolane, dithiolane, morpholine, thiomorpholine, dioxane, or dithiane. The heterocyclyl groups can also be fused to aromatic or non-aromatic ring systems to form members including, but not limited to, indoline. Heterocyclyl groups can be unsubstituted or substituted. For example, “substituted heterocyclyl” groups can be substituted with one or more groups selected from halo, hydroxy, amino, oxo, alkylamino, amido, acyl, nitro, cyano, and alkoxy.

[0027] The heterocyclyl groups can be linked via any position on the ring. For example, aziridine can be 1- or 2-aziridine, azetidine can be 1- or 2- azetidine, pyrrolidine can be 1-, 2- or 3-pyrrolidine, piperidine can be 1-, 2-, 3- or 4-piperidine, pyrazolidine can be 1-, 2-, 3-, or 4-pyrazolidine, imidazolidine can be 1-, 2-, 3- or 4-imidazolidine, piperazine can be 1-, 2-, 3- or 4-piperazine, tetrahydrofuran can be 1- or 2-tetrahydrofuran, oxazolidine can be 2-, 3-, 4- or 5-oxazolidine, isoxazolidine can be 2-, 3-, 4- or 5-isoxazolidine, thiazolidine can be 2-, 3-, 4- or 5-thiazolidine, isothiazolidine can be 2-, 3-, 4- or 5- isothiazolidine, and morpholine can be 2-, 3- or 4-morpholine.

[0028] When heterocyclyl includes 3 to 8 ring members and 1 to 3 heteroatoms, representative members include, but are not limited to, pyrrolidine, piperidine, tetrahydrofuran, oxane, tetrahydrothiophene, thiane, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, morpholine, thiomorpholine, dioxane and dithiane. Heterocyclyl can also form a ring having 5 to 6 ring members and 1 to 2 heteroatoms, with representative members including, but not limited to, pyrrolidine,

piperidine, tetrahydrofuran, tetrahydrothiophene, pyrazolidine, imidazolidine, piperazine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, and morpholine.

[0029] As used herein, the term “protecting group” refers to a chemical moiety that renders a functional group (*e.g.*, an amino group) unreactive, but is also removable so as to restore the amino group. Examples of protecting groups include, but are not limited to, benzyloxycarbonyl (Z or Cbz); 9-fluorenylmethyloxycarbonyl (Fmoc); *tert*-butyloxycarbonyl (Boc); allyloxycarbonyl (Alloc); *p*-toluene sulfonyl (Tos); 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc); 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl (Pbf); mesityl-2-sulfonyl (Mts); 4-methoxy-2,3,6-trimethylphenylsulfonyl (Mtr); acetamido; phthalimido; and the like. Other protecting groups are known to those of skill in the art including, for example, those described by Green and Wuts (*Protective Groups in Organic Synthesis*, 4th Ed. 2007, Wiley-Interscience, New York).

[0030] As used herein, the term “carbonyl,” by itself or as part of another substituent, refers to C(O)- , *i.e.*, a carbon atom double-bonded to oxygen and bound to two other groups in the moiety having the carbonyl.

[0031] As used herein, the term “amino” refers to a moiety NR_2 , wherein each R group is H or alkyl. An amino moiety can be ionized to form the corresponding ammonium cation. “Dialkylamino” refers to an amino moiety wherein each R group is alkyl.

[0032] As used herein, the term “sulfonyl” refers to a moiety SO_2R , wherein the R group is alkyl, haloalkyl, or aryl. An amino moiety can be ionized to form the corresponding ammonium cation. “Alkylsulfonyl” refers to an amino moiety wherein the R group is alkyl.

[0033] As used herein, the term “hydroxy” refers to the moiety OH .

[0034] As used herein, the term “cyano” refers to a carbon atom triple-bonded to a nitrogen atom (*i.e.*, the moiety $\text{C}\equiv\text{N}$).

[0035] As used herein, the term “carboxy” refers to the moiety C(O)OH . A carboxy moiety can be ionized to form the corresponding carboxylate anion.

[0036] As used herein, the term “amido” refers to a moiety NRC(O)R or C(O)NR_2 , wherein each R group is H or alkyl.

[0037] As used herein, the term “nitro” refers to the moiety NO_2 .

[0038] As used herein, the term “oxo” refers to an oxygen atom that is double-bonded to a compound (*i.e.*, O=).

[0039] In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents are generally those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein. In general, “substituted,” as used herein, does not encompass replacement and/or alteration of a key functional group by which a molecule is identified, *e.g.*, such that the “substituted” functional group becomes, through substitution, a different functional group. For example, a “substituted phenyl” group must still comprise the phenyl moiety and cannot be modified by substitution, in this definition, to become, *e.g.*, a cyclohexyl group.

[0040] Examples of suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^a$; $-(CH_2)_{0-4}OR^a$; $-O(CH_2)_{0-4}R^a$; $-O-(CH_2)_{0-4}C(O)OR^a$; $-(CH_2)_{0-4}CH(OR^a)_2$; $-(CH_2)_{0-4}SR^a$; $-(CH_2)_{0-4}Ph$, wherein Ph is phenyl which may be substituted with R^a ; $-(CH_2)_{0-4}O(CH_2)_{0-1}phenyl$, which phenyl may be substituted with R^a ; $-CH=CHPh$, wherein Ph is phenyl which may be substituted with R^a ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Py$, wherein Py is pyridyl which may be substituted with R^a ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^a)_2$; $-(CH_2)_{0-4}N(R^a)C(O)R^a$; $-N(R^a)C(S)R^a$; $-(CH_2)_{0-4}N(R^a)C(O)NR^a_2$; $-N(R^a)C(S)NR^a_2$; $-(CH_2)_{0-4}N(R^a)C(O)OR^a$; $-N(R^a)N(R^a)C(O)R^a$; $-N(R^a)N(R^a)C(O)NR^a_2$; $-N(R^a)N(R^a)C(O)OR^a$; $-(CH_2)_{0-4}C(O)R^a$; $-C(S)R^a$; $-(CH_2)_{0-4}C(O)OR^a$; $-(CH_2)_{0-4}C(O)SR^a$; $-(CH_2)_{0-4}C(O)OSiR^a_3$; $-(CH_2)_{0-4}OC(O)R^a$; $-OC(O)(CH_2)_{0-4}SR-SC(S)SR^a$; $-(CH_2)_{0-4}SC(O)R^a$; $-(CH_2)_{0-4}C(O)NR^a_2$; $-C(S)NR^a_2$; $-C(S)SR^a$; $-SC(S)SR^a$; $-(CH_2)_{0-4}OC(O)NR^a_2$; $-C(O)N(OR^a)R^a$; $-C(O)C(O)R^a$; $-C(O)CH_2C(O)R^a$; $-C(NOR^a)R^a$; $-(CH_2)_{0-4}SSR^a$; $-(CH_2)_{0-4}S(O)_2R^a$; $-(CH_2)_{0-4}S(O)_2OR^a$; $-(CH_2)_{0-4}OS(O)_2R^a$; $-S(O)_2NR^a_2$; $-(CH_2)_{0-4}S(O)R^a$; $-N(R^a)S(O)_2NR^a_2$; $-N(R^a)S(O)_2R^a$; $-N(OR^a)R^a$; $-C(NH)NR^a_2$; $-P(O)_2R^a$; $-P(O)R^a_2$; $-OP(O)R^a_2$; $-OP(O)(OR^a)_2$; SiR^a_3 ; $-(C_{1-4} \text{ straight or branched})alkylene-$

O-N(R^a)₂; or -(C₁₋₄ straight or branched)alkylene)C(O)O-N(R^a)₂. Each R^a is independently hydrogen; C₁₋₆ alkyl; -CH₂Ph; -O(CH₂)₀₋₁Ph; -CH₂-(5- to 6-membered heteroaryl); C₃₋₈ cycloalkyl; C₆₋₁₀ aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl; and each R^a may be further substituted as described below.

- 5 **[0041]** Examples of suitable monovalent substituents on R^a are independently halogen, -(CH₂)₀₋₂R^b; -(CH₂)₀₋₂OH; -(CH₂)₀₋₂OR^b; -(CH₂)₀₋₂CH(OR^b)₂; -CN; -N₃; -(CH₂)₀₋₂C(O)R^b; -(CH₂)₀₋₂C(O)OH; -(CH₂)₀₋₂C(O)OR^b; -(CH₂)₀₋₂SR^b; -(CH₂)₀₋₂SH; -(CH₂)₀₋₂NH₂; -(CH₂)₀₋₂NHR^b; -(CH₂)₀₋₂NR^b₂; -NO₂; SiR^b₃; -OSiR^b₃; -C(O)SR^b; -(C₁₋₄ straight or branched alkylene)C(O)OR^b; or -SSR^b; wherein each R^b is independently selected
10 from C₁₋₄ alkyl; -CH₂Ph; -O(CH₂)₀₋₁Ph; C₃₋₈ cycloalkyl; C₆₋₁₀ aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl. Suitable divalent substituents on a saturated carbon atom of R^a include =O and =S.

- [0042]** Examples of suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: =O; =S; =NNR^γ₂; =NNHC(O)R^γ; =NNHC(O)OR^γ; =NNHS(O)₂R^γ; =NR^γ; =NOR^γ; -O(C(R^γ)₂)₂₋₃O-; or -S(C(R^γ)₂)₂₋₃S-; wherein
15 each independent occurrence of R^γ is selected from hydrogen; C₁₋₆ alkyl, which may be substituted as defined below; C₃₋₈ cycloalkyl; C₆₋₁₀ aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: -O(CR^b)₂₋₃O-; wherein
20 each independent occurrence of R^b is selected from hydrogen; C₁₋₆ alkyl which may be substituted as defined below; C₃₋₈ cycloalkyl; C₆₋₁₀ aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl.

- [0043]** Examples of suitable substituents on the alkyl group of R^γ include halogen; -R^δ; -OH; -OR^δ; -CN; -C(O)OH; -C(O)OR^δ; -NH₂; -NHR^δ; -NR^δ₂; or -NO₂; wherein each R^δ
25 is independently C₁₋₄ alkyl; -CH₂Ph; -O(CH₂)₀₋₁Ph; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl.

- [0044]** Examples of suitable substituents on a substitutable nitrogen of an “optionally substituted” group include -R^ε; -NR^ε₂; -C(O)R^ε; -C(O)OR^ε; -C(O)C(O)R^ε; -C(O)CH₂C(O)R^ε; -S(O)₂R^ε; -S(O)₂NR^ε₂; -C(S)NR^ε₂; -C(NH)NR^ε₂; or -N(R^ε)S(O)₂R^ε; wherein each R^ε is
30 independently hydrogen; C₁₋₆ alkyl which may be substituted as defined below; C₃₋₈ cycloalkyl; C₆₋₁₀ aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl.

[0045] Examples of suitable substituents on the alkyl group of R^e are independently halogen; $-R^{\delta}$; $-OH$; $-OR^{\delta}$; $-CN$; $-C(O)OH$; $-C(O)OR^{\delta}$; $-NH_2$; $-NHR^{\delta}$; $-NR^{\delta}_2$; or $-NO_2$; wherein each R^{δ} is independently C_{1-4} alkyl; $-CH_2Ph$; $-O(CH_2)_{0-1}Ph$; C_{6-10} aryl; 4- to 10-membered heterocyclyl; or 6- to 10-membered heteroaryl.

5 [0046] As used herein, the term “pharmaceutically acceptable excipient” refers to a substance that aids the administration of an active agent to a subject. By “pharmaceutically acceptable,” it is meant that the excipient is compatible with the other ingredients of the formulation and is not deleterious to the recipient thereof. Pharmaceutical excipients useful
10 lubricants, glidants, coatings, sweeteners, flavors and colors.

[0047] As used herein, the term “salt” refers to acid or base salts of the compounds of the invention. Illustrative examples of pharmaceutically acceptable salts are mineral acid (hydrochloric acid, hydrobromic acid, phosphoric acid, and the like) salts, organic acid (acetic acid, propionic acid, glutamic acid, citric acid and the like) salts, and quaternary
15 ammonium (methyl iodide, ethyl iodide, and the like) salts. It is understood that the pharmaceutically acceptable salts are non-toxic.

[0048] Pharmaceutically acceptable salts of the acidic compounds of the present invention are salts formed with bases, namely cationic salts such as alkali and alkaline earth metal salts (such as sodium, lithium, potassium, calcium, and magnesium salts), as well as ammonium
20 salts (such as ammonium, trimethyl-ammonium, diethylammonium, and tris-(hydroxymethyl)-methyl-ammonium salts).

[0049] Similarly acid addition salts, such as of mineral acids, organic carboxylic and organic sulfonic acids, *e.g.*, hydrochloric acid, methanesulfonic acid, maleic acid, are also possible provided a basic group, such as pyridyl, constitutes part of the structure.

25 [0050] The neutral forms of the compounds can be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are eq to the parent form of the compound for the purposes of the present invention.

30 [0051] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily

undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0052] As used herein, the terms “*Porphyromonas gingivalis*” and “*P. gingivalis*” refer to the gram-negative asaccharolytic bacterium that is recognized as a key causative microbe in the pathogenesis of periodontitis and related conditions. “*P. gingivalis* infection” refers to the invasion and colonization of *P. gingivalis* in a bodily tissue such as the gums or the brain. *P. gingivalis* infection is frequently characterized by subsequent tissue injury and disease.

[0053] As used herein, the term “gingipain” refers to cysteine proteases expressed by *P. gingivalis* having trypsin-like specificity (*i.e.*, Lys-Xaa and Arg-Xaa). Gingipains are recognized as the major virulence factors of *P. gingivalis* and contribute to bacterial attachment and colonization, nutrient acquisition, evasion of host defenses, and tissue invasion. The terms “arginine gingipain” and “Rgp” are used interchangeably to refer to the *P. gingivalis* arginine-specific gingipains RgpA and RgpB, classified under EC number EC 3.4.22.37. The rgpA and rgpB gene-translation products, RgpA and RgpB, share a caspase-like protease domain (specific for Arg-Xaa peptide bonds) and an immunoglobulin-like domain. In RgpA, the protease and immunoglobulin-like domains are followed by a large C-terminal extension containing hemagglutinin-adhesin domains.

[0054] As used herein, the term “inhibiting” refers to reducing the level of activity (*e.g.*, proteolytic activity) of an enzyme such as a gingipain which can be assessed, for example, using an *in vitro* assay or other suitable assay. Inhibition of enzyme activity caused by a particular substance (*e.g.*, a gingipain inhibitor as described herein) can be expressed as the percentage of the enzyme activity measured in the absence of the substance under similar conditions. The ability of a particular substance to inhibit an enzyme can be expressed as an IC₅₀ value, *i.e.*, the concentration of the compound required to reduce the activity of the enzyme to 50% of its maximum activity.

[0055] As used herein, the terms “treat,” “treatment,” and “treating” refer to any indicia of success in the treatment or amelioration of an injury, pathology, condition, or symptom (*e.g.*, cognitive impairment), including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the symptom, injury, pathology or condition

more tolerable to the patient; reduction in the rate of symptom progression; decreasing the frequency or duration of the symptom or condition; or, in some situations, preventing the onset of the symptom. The treatment or amelioration of symptoms can be based on any objective or subjective parameter, including, *e.g.*, the result of a physical examination.

5 **[0056]** As used herein, the terms “effective amount” and “therapeutically effective amount” refer to a dose of a compound such as an Rgp inhibitor that inhibits the activity of a gingipain and/or produces therapeutic effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992);
10 Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); *Goodman & Gilman’s The Pharmacological Basis of Therapeutics*, 11th Edition, 2006, Brunton, Ed., McGraw-Hill; and *Remington: The Science and Practice of Pharmacy*, 21st Edition, 2005, Hendrickson, Ed., Lippincott, Williams & Wilkins).

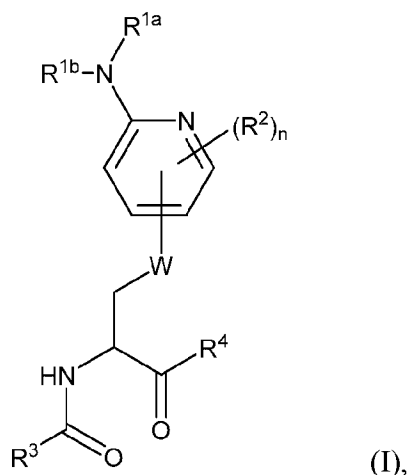
15 **[0057]** As used herein, the term “Alzheimer’s disease” refers to a progressive disease of the central nervous system in humans and other mammals. It is manifested by dementia (especially in the elderly); disorientation; loss of memory; difficulty with language, calculation, or visual-spatial skills; and psychiatric manifestations. Alzheimer’s disease is associated with progressive neurodegeneration and characteristic pathology, namely beta
20 amyloid plaques and tau tangles.

[0058] As used herein, the term “osteoarthritis” refers to a chronic degenerative joint disease that results from breakdown of joint cartilage, synovial tissue, and underlying bone.

[0059] As used herein, the term “subject” refers to animals such as mammals, including, but not limited to, primates (*e.g.*, humans), cows, sheep, goats, horses, dogs, cats, rabbits,
25 rats, mice and the like.

III. Gingipain inhibitors

[0060] In one embodiment, the invention provides a compound according to Formula I:



or a pharmaceutically acceptable salt thereof, wherein

W is selected from a bond, CH₂, and O;

R^{1a} and R^{1b} are independently selected from H and C₁₋₆ alkyl;

5 R² is selected from C₁₋₆ alkyl and halogen;

subscript n is 0 or 1;

R³ is selected from C₃₋₈ alkyl, C₃₋₈ cycloalkyl, C₃₋₁₂ heterocyclyl, C₆₋₁₀ aryl, and

C₅₋₁₂ heteroaryl wherein R³ is optionally substituted with one or more R^{3a} substituents;

10 each R^{3a} is independently selected from halogen, -CN, -NO₂, -N₃, -OH, C₁₋₄ alkyl,

C₁₋₄ haloalkyl, C₁₋₄ alkoxy,

C₁₋₄ haloalkoxy, -N(R^c)₂, -(CH₂)_kC(O)R^b, -NR^c(CH₂)_uC(O)R^b,

-O(CH₂)_uC(O)R^b, -(CH₂)_kCONR^cR^c, -(CH₂)_kNR^cC(O)R^b,

-NR^c(CH₂)_uCONR^cR^c, -NR^c(CH₂)_uNR^cC-(O)R^b, -O(CH₂)_uCONR^cR^c,

15 and -O(CH₂)_uNR^cC(O)R^b, and optionally substituted triazolyl;

each R^b is independently selected from C₁₋₄ alkyl, C₁₋₄ haloalkyl, and

C₁₋₄ deuterioalkyl;

each R^c is independently selected from hydrogen and C₁₋₈ alkyl;

each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6;

20 each subscript u is independently selected from 1, 2, 3, 4, 5, and 6;

R⁴ is selected from -CH₂R^{4a} and C₁₋₆ haloalkyl;

R^{4a} is selected from -O-R⁵, -S-R⁶, -SO-R⁶, -SO₂-R⁶, -N(R⁷)₂, and C₅₋₁₂ heteroaryl;

R⁵ is selected from phenyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₅₋₁₂ heteroaryl,

wherein phenyl is substituted with 1-5 halogens, and

wherein C₅₋₁₂ heteroaryl is optionally substituted with halogen or C₁₋₃ haloalkyl;

R⁶ is selected from phenyl, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₅₋₁₂ heteroaryl,

wherein phenyl is optionally substituted with 1-5 halogens, and

5 wherein C₅₋₁₂ heteroaryl is optionally substituted with halogen or C₁₋₃ haloalkyl; and

each R⁷ is independently selected C₁₋₆ alkyl.

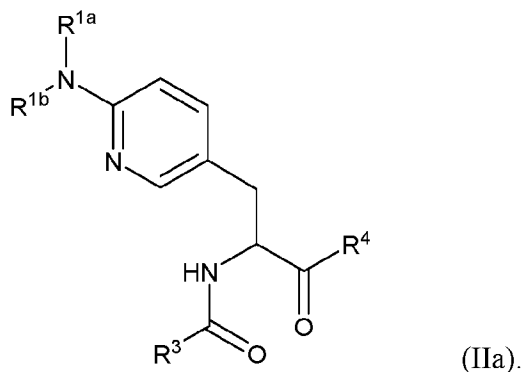
[0061] In some embodiments, each of R^{1a} and R^{1b} is independently selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, each of R^{1a} is H and R^{1b} is
10 selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, R^{1b} is independently selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl and R^{1a} is H. In
15 some embodiments, R^{1a} and R^{1b} are H.

[0062] Compounds of the invention can be prepared in protected form (*e.g.*, protected compounds wherein at least one of R^{1a} and R^{1b} is an amine protecting group). A number of suitable protecting groups—as described, for example, by Green and Wuts (*Protective Groups in Organic Synthesis*, 4th Ed. 2007, Wiley-Interscience, New York)—can be used. In
20 some embodiments, R^{1a} is H and R^{1b} is selected from benzyloxycarbonyl; 9-fluorenylmethyl-oxycarbonyl; *tert*-butyloxycarbonyl; and allyloxycarbonyl. In some embodiments, R^{1a} and R^{1b} are selected from benzyloxycarbonyl; 9-fluorenylmethyl-oxycarbonyl; *tert*-butyloxycarbonyl; and allyloxycarbonyl. In some embodiments, R^{1a} is H and R^{1b} is *tert*-butyloxycarbonyl. Compounds can also be prepared in alkylated form (*i.e.*, compounds
25 wherein at least one of R^{1a} and R^{1b} is an alkyl group). One or both of R^{1a} and R^{1b} can be, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, or *t*-butyl.

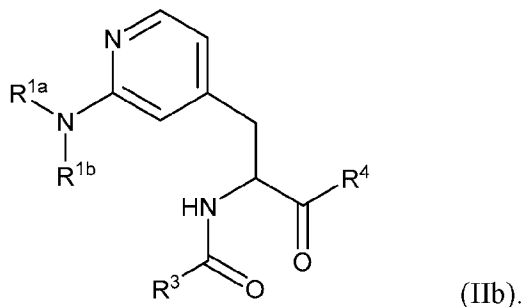
[0063] In some embodiments, subscript *n* is 0. In some embodiments, subscript *p* is 1. In some embodiments, subscript *n* is 1 and R² is selected from fluoro, chloro, bromo, iodo, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, subscript *n* is 1 and R² is
30 selected from fluoro, chloro, and methyl. In some embodiments, subscript *n* is 2 or 3.

[0064] In some embodiments, W is a bond. In some embodiments, W is selected from CH₂ and O.

[0065] In some embodiments, the compound has a structure according to Formula IIa:



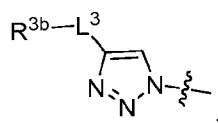
5 [0066] In some embodiments, the compound has a structure according to Formula IIb:



[0067] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R³ is selected from C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₅₋₁₂ heteroaryl, and C₃₋₁₂ heterocyclyl, each of which is optionally substituted with one or more R^{3a} substituents. For example, R³ can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl. In some embodiments, R³ is selected from cyclobutyl, cyclopentyl, and cyclohexyl. In some embodiments, R³ is selected from phenyl and naphthyl. In some embodiments, R³ is selected from pyrrolyl, pyridinyl, imidazolyl, pyrazolyl, triazolyl, pyrazinyl, triazinyl, indolyl, isoindolyl, and quinoliny. In some such embodiments, R³ is selected from cyclopentyl and phenyl, each of which is optionally substituted with one or more R^{3a} substituents. In some such embodiments, each R^{3a} is independently selected from halogen, -N₃, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and -NR^cC(O)R^b. In some embodiments, R³ is cyclopentyl.

[0068] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^3 is selected from C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, C₅₋₁₂ heteroaryl, and C₃₋₁₂ heterocyclyl, each of which is optionally substituted with one or more R^{3a} substituents. In some such embodiments, R^3 is selected from cyclopentyl and phenyl, each of which is optionally substituted with one or more R^{3a} substituents. In some such embodiments, each R^{3a} is independently selected from halogen, -N₃, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkoxy, and -NR^cC(O)R^b. In some embodiments, R^3 is cyclopentyl.

[0069] One of skill in the art will appreciate that compounds containing azide groups (*e.g.*, compounds wherein R^{3a} is -N₃) can be modified with further functional groups via reaction with a complementary reaction partner such as an alkyne-bearing compound or a phosphine-bearing compound. Reaction of azides and alkynes via [3+2] cycloaddition, commonly referred to as “click chemistry,” can be used to install a variety of substituted triazole groups in the compounds of the invention. Accordingly, some embodiments of the invention provide compounds wherein R^{3a} is an optionally substituted triazolyl moiety according to the formula:



wherein R^{3b} is a functional moiety and L^3 is a linking moiety.

[0070] In some embodiments, the linking moiety L^3 has a structure - L^{3a} - L^{3b} -, wherein L^{3a} and L^{3b} are independently selected from a bond, a divalent polymer moiety, and linear or branched, saturated or unsaturated C₁₋₃₀ alkyl; wherein:

one or more carbon atoms in the C₁₋₃₀ alkyl is optionally and independently replaced by O, S, NR^a;

two or more groupings of adjacent carbon atoms in the C₁₋₃₀ alkyl are optionally and independently replaced by -NR^a(CO)- or -(CO)NR^a-; and

two or more groupings of adjacent carbon atoms in the C₁₋₃₀ alkyl are optionally and independently replaced by a 4- to 8-membered, divalent carbocycle or a 4- to 8-membered, divalent heterocycle having one to four heteroatoms selected from O, S, and N; and

each R^a is independently selected from H and C₁₋₆ alkyl.

[0071] In some embodiments, the functional group R^{3b} is selected from a chromophore, a fluorophore, and a binding moiety (*e.g.*, biotin, glutathione, and the like).

[0072] In some embodiments, R^3 is selected from C_{3-8} alkyl and C_{3-8} cycloalkyl, each of which is optionally substituted with one or more R^{3a} substituents. In some embodiments, R^3 is selected from cyclopentyl and isopropyl. In some embodiments, R^3 is unsubstituted cyclopentyl. In some embodiments, R^3 is isopropyl and R^{3a} is methoxy.

[0073] In certain embodiments, R^3 and the carbonyl to which it is bonded form a moiety other than a naturally-occurring amino acid residue (an L amino acid residue) or an isomer of a naturally-occurring amino acid residue (a D amino acid residue). In some embodiments, R^3 and the carbonyl to which it is bonded form a moiety other than asparaginy, substituted asparaginy, glutaminy (*i.e.*, a glutamine residue), substituted glutaminy (*i.e.*, a substituted glutamine residue), glutamyl (*i.e.*, a glutamic acid residue), substituted glutamyl (*i.e.*, a substituted glutamic acid residue), isoleuciny, substituted isoleuciny, leuciny, substituted leuciny, lysiny, substituted lysiny, methioniny, substituted methioniny, proliny, substituted proliny, threoniny, substituted threoniny, valiny, or substituted valiny. The substituted amino acid residues may be present in larger peptide groups having two or more amino acid residues linked via amine bonds.

[0074] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from $-S-R^6$, $-SO-R^6$, $-SO_2-R^6$, C_{5-12} heteroaryl, and $-N-R^7$. In some embodiments, R^{4a} is selected from $-O-R^5$, C_{5-12} heteroaryl, and $-N-(R^7)_2$. In some embodiments, R^{4a} is selected from $-O-R^5$, $-S-R^6$, $-SO-R^6$, $-SO_2-R^6$, and $-N-(R^7)_2$. In some embodiments, R^{4a} is selected from $-O-R^5$, $-S-R^6$, $-SO-R^6$, $-SO_2-R^6$, and C_{5-12} heteroaryl.

[0075] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C_{1-6} haloalkoxy, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{1-6} alkylsufonyl, $(C_{1-6}$ dialkyl)amino, C_{5-12} heteroaryl, $-O$ -phenyl wherein phenyl is substituted with 1-5 halogens, and $-S$ -phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0076] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkylthio, C_{1-6} alkylsufonyl, $(C_{1-6}$ dialkyl)amino,

C₅₋₁₂ heteroaryl, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0077] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ haloalkythio, C₁₋₆ alkylsulfonyl, (C₁₋₆ dialkyl)amino, C₅₋₁₂ heteroaryl, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0078] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfonyl, (C₁₋₆ dialkyl)amino, C₅₋₁₂ heteroaryl, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0079] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkythio, (C₁₋₆ dialkyl)amino, C₅₋₁₂ heteroaryl, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0080] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkythio, C₁₋₆ alkylsulfonyl, C₅₋₁₂ heteroaryl, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0081] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkythio, C₁₋₆ alkylsulfonyl, (C₁₋₆ dialkyl)amino, -O-phenyl wherein phenyl is substituted with 1-5 halogens, and-S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0082] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkythio, C₁₋₆ alkylsulfonyl, (C₁₋

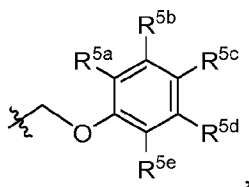
₆ dialkyl)amino, C₅₋₁₂ heteroaryl, and -S-phenyl wherein phenyl is optionally substituted with 1-5 halogens.

[0083] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkylthio, C₁₋₆ alkylsulfonyl, (C₁₋₆ dialkyl)amino, C₅₋₁₂ heteroaryl, and -O-phenyl wherein phenyl is substituted with 1-5 halogens.

[0084] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R⁴ is -CH₂-O-R⁵ and R⁵ is selected from 1,1,1,3,3,3-hexafluoroprop-2-yl, isoxazolyl, and phenyl, wherein phenyl is substituted with 1-5 halogens.

[0085] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R⁵ is phenyl substituted with 1-5 halogens. In some embodiments, each halogen in R⁵ is selected from F and Cl. In some embodiments, each halogen in R⁵ is F.

[0086] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is -OR⁵, such that R⁴ is a moiety having the structure:



wherein R^{5a}, R^{5b}, R^{5c}, R^{5d}, and R^{5e} are independently selected from hydrogen and halogen, and the wavy line represents the point of connection to the compound.

[0087] In some embodiments:

R^{5a} is halogen, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is halogen, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is halogen, R^{5d} is H, and R^{5e} is H; or

R^{5a} is halogen, R^{5b} is H, R^{5c} is H, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is H, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is H, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is H, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is halogen, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is H, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is H, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is halogen, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is H, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is H, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is H, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is H, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is H, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is H, and R^{5e} is halogen; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is halogen, R^{5d} is halogen, and R^{5e} is H; or
 R^{5a} is halogen, R^{5b} is halogen, R^{5c} is H, R^{5d} is halogen, and R^{5e} is halogen.

[0088] In some embodiments:

R^{5a} is F or Cl, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is F or Cl; or

R^{5a} is H, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is H; or
5 R^{5a} is H, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is H, and R^{5e} is F or Cl; or
10 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is F or Cl; or
15 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is H, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is H, R^{5c} is F or Cl, R^{5d} is F or Cl, and R^{5e} is F or Cl; or
20 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is F or Cl, R^{5d} is H, and R^{5e} is F or Cl; or
 R^{5a} is F or Cl, R^{5b} is F or Cl, R^{5c} is H, R^{5d} is F or Cl, and R^{5e} is F or Cl.

[0089] In some embodiments:

R^{5a} is F, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
25 R^{5a} is H, R^{5b} is H, R^{5c} is F, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is F, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is F, R^{5c} is H, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is F, R^{5b} is H, R^{5c} is F, R^{5d} is H, and R^{5e} is H; or
30 R^{5a} is F, R^{5b} is H, R^{5c} is H, R^{5d} is F, and R^{5e} is H; or
 R^{5a} is F, R^{5b} is H, R^{5c} is H, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is F, R^{5c} is F, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F, R^{5c} is H, R^{5d} is F, and R^{5e} is H; or

5 R^{5a} is H, R^{5b} is F, R^{5c} is H, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F, R^{5d} is F, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is H, R^{5c} is H, R^{5d} is F, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is F, R^{5c} is F, R^{5d} is H, and R^{5e} is H; or
 R^{5a} is F, R^{5b} is F, R^{5c} is H, R^{5d} is F, and R^{5e} is H; or
 R^{5a} is F, R^{5b} is F, R^{5c} is H, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is H, R^{5c} is F, R^{5d} is F, and R^{5e} is H; or
 10 R^{5a} is F, R^{5b} is H, R^{5c} is F, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is H, R^{5c} is H, R^{5d} is F, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is F, R^{5c} is F, R^{5d} is F, and R^{5e} is H; or
 R^{5a} is H, R^{5b} is F, R^{5c} is F, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is F, R^{5c} is H, R^{5d} is F, and R^{5e} is F; or
 R^{5a} is H, R^{5b} is H, R^{5c} is F, R^{5d} is F, and R^{5e} is F; or
 15 R^{5a} is H, R^{5b} is F, R^{5c} is F, R^{5d} is F, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is H, R^{5c} is F, R^{5d} is F, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is F, R^{5c} is F, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is F, R^{5c} is F, R^{5d} is H, and R^{5e} is F; or
 R^{5a} is F, R^{5b} is F, R^{5c} is H, R^{5d} is F, and R^{5e} is F.

20 **[0090]** In certain embodiments, R^4 is not 2,3,5,6-tetrafluorophenoxymethyl.

[0091] In some embodiments, the invention provides compounds of Formula I, Formula
 IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^5 is selected
 from 2-fluorophenyl; 3-fluorophenyl; 4-fluorophenyl; 2,3-difluorophenyl; 2,4-
 difluorophenyl; 2,5-difluorophenyl; 2,6-difluorophenyl; 3,4-difluorophenyl; 3,5-
 25 difluorophenyl; 2,3,4-trifluorophenyl; 3,4,5-trifluorophenyl; 2,3,6-trifluorophenyl; 2,3,5-
 trifluorophenyl; and 2,3,5,6-tetrafluorophenyl.

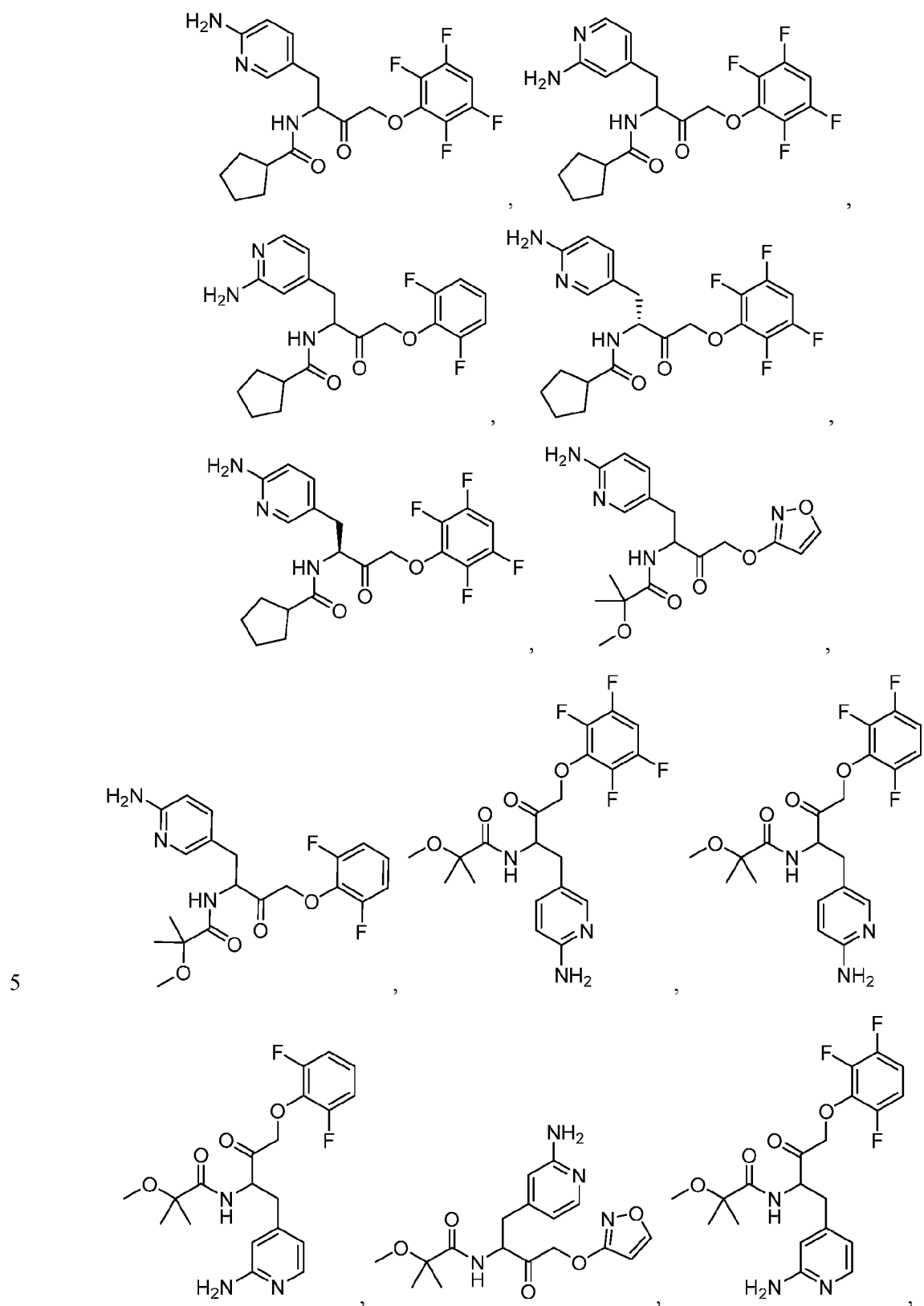
[0092] In some embodiments, the invention provides compounds of Formula I, Formula
 IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^5 is selected
 from 2,6-difluorophenyl; 2,3,6-trifluorophenyl; and 2,3,5,6-tetrafluorophenyl.

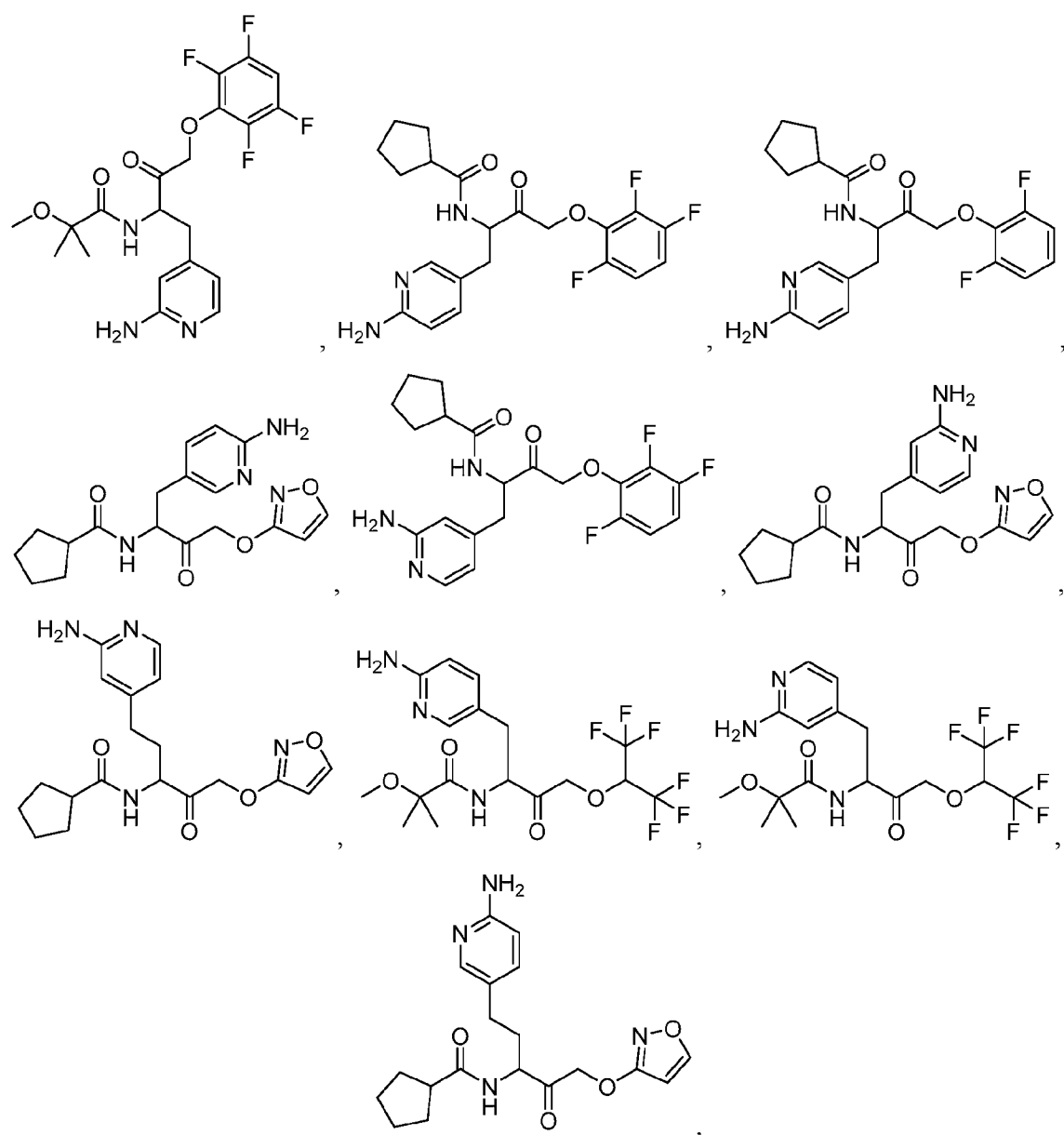
30 **[0093]** In some embodiments, the invention provides compounds of Formula I, Formula
 IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is
 C_{5-12} heteroaryl. R^{4a} can be, for example, pyrrolyl, pyridinyl, imidazolyl, pyrazolyl, triazolyl,

tetrazolyl, pyrazinyl, triazinyl, indolyl, isoindolyl, or quinolinyl. In some embodiments, R^{4a} is isoxazolyl.

- [0094] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is –O-R⁵,
5 wherein R⁵ is C₁₋₆ haloalkyl. In such embodiments, R⁵ can be, *e.g.*, chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trichloroethyl, 2,2,2-trifluoroethyl, pentachloroethyl, pentafluoroethyl, 1,1,1,3,3,3-hexachloropropyl, 1,1,1,3,3,3-hexafluoropropyl, or the like. In some embodiments, R⁵ is 1,1,1,3,3,3-hexafluoroprop-2-yl.
- 10 [0095] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is selected from –S-R⁶ and –SO₂-R⁶, wherein R⁶ is C₁₋₆ alkyl. In such embodiments, R⁶ can be, *e.g.*, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec butyl, tert butyl, pentyl, isopentyl, or hexyl.
- 15 [0096] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R^{4a} is –N(R⁷)₂, wherein each R⁷ is independently selected C₁₋₆ alkyl. In such embodiments, each R⁷ can independently be, *e.g.*, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec butyl, tert butyl, pentyl, isopentyl, or hexyl.
- 20 [0097] In some embodiments, the invention provides compounds of Formula I, Formula IIa, and/or Formula IIb, and pharmaceutically acceptable salts thereof, wherein R⁴ is haloalkyl. For example, R⁵ can be chloromethyl, dichloromethyl, trichloromethyl, difluoromethyl, or trifluoromethyl.
- [0098] The compounds of the invention can be further substituted; a compound according to Formula I may contain, for example, an optionally substituted R^{1a} and/or R^{1b} group, one or
25 more optionally substituted R² groups, an optionally substituted R³ group, and/or an optionally substituted R⁴ group (including, an optionally substituted R⁵ group, an optionally substituted R⁶ group, and/or one or more optionally substituted R⁷ groups).

[0099] In some embodiments, the aminopyridyl ketone compound is selected from:

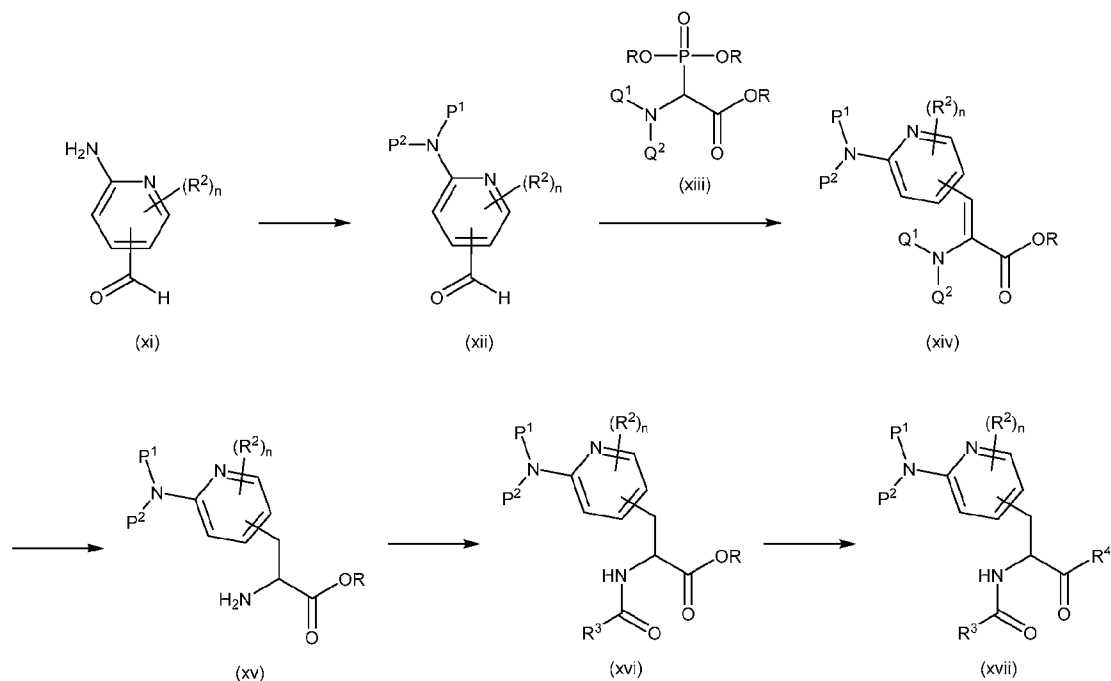




5 and pharmaceutically acceptable salts thereof.

[0100] Aminopyridyl ketones may be prepared by the following approaches, summarized in Scheme 1 and described below. As shown in Scheme 1, aminopyridines (*e.g.*, 2-amino-4-formylpyridine and 2-amino-5-formylpyridine (xi)) can be reacted with a suitable protecting reagent (*e.g.*, di-*tert*-butyl dicarbonate) to prepare the corresponding mono- and/or di-protected formylpyridines (xii), wherein P¹ is H or a protecting group and P² is a protecting group. Any of these aldehydes (xii) may be reacted with a protected phosphonate (xiii) (wherein Q¹ is H or a protecting group; Q² is a protecting group; and each R is independently C₁₋₆ alkyl; *e.g.*, ZHNCH(CO₂Me)PO₃Me₂) and a strong base to prepare dehydro-aminopyridylalanine methyl esters (xiv).

Scheme 1



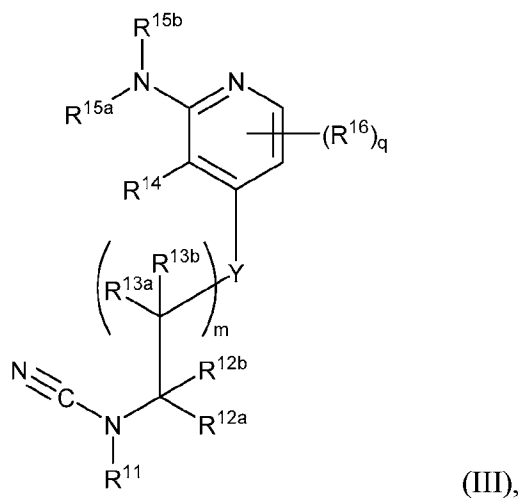
[0101] When Q^1 and/or Q^2 is a Z group (or another protecting group which can be removed by hydrogenation), dehydro-aminopyridylalanines (xiv) may be hydrogenated in the presence of palladium on carbon, providing aminoesters (xv) by simultaneously saturating the olefins and deprotecting the α -amino group. The free amino groups may be reacted with carboxylic acids ($R^3C(O)OH$) and dehydrating agents to form amidoesters (xvi). The dehydrating agent may be HATU or any of many other reagents suitable for carboxamide formation. The amidoesters may be converted to protected products (xvii) by various routes. In one non-limiting example, the amidoesters are hydrolyzed using a strong based such as NaOH. The resulting carboxylic acids are then reacted with $ClCO_2Et$, a tertiary amine, and diazo methane to form diazomethyl ketones, which can then be treated with HBr to give bromomethyl ketones. In another sequence, the methyl esters may be treated with $ClCH_2I$ and $LiN(iPr)_2$ to provide chloromethyl ketones in one step. The bromomethyl ketones or chloromethyl ketones can be heated with substituted phenols and KF in DMF to give aryloxymethyl ketones. In another non-limiting example, the bromomethyl or chloromethyl ketones are treated with isoxazole-5-one and KF in DMF to give isoxazolyloxymethyl ketones. Lastly, the protecting groups P^1 and P^2 (e.g., Boc groups) may be removed under suitable conditions (e.g., via treatment with trifluoroacetic acid), to afford the desired final products.

[0102] The starting materials and reagents used in preparing the compounds of the invention are either available from commercial suppliers or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's *Reagents for Organic Synthesis, Vol. 1-28* (Wiley, 2016); March's *Advanced Organic Chemistry, 7th Ed.* (Wiley, 2013); and Larock's *Comprehensive Organic Transformations, 2nd Ed.* (Wiley, 1999). The starting materials and the intermediates of the reaction can be isolated and purified if desired using conventional techniques including, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials can be characterized using conventional means, including measuring physical constants and obtaining spectral data.

[0103] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range of from about -78 °C to about 250 °C. For example, reactions can be conducted at from about 0 °C to about 125 °C, or at about room (or ambient) temperature, *e.g.*, about 20 °C. In some embodiments, reactions are conducted at about 0 °C, 20 °C, 25 °C, 90 °C, 100 °C, 110 °C, 125 °C, 150 °C, 175 °C, or 200 °C. In some embodiments, reactions are conducted starting at a first temperature (*e.g.*, about -78 °C or about 0 °C), and allowed to warm to a higher second temperature (*e.g.*, about 20 °C or about 25 °C). One of skill in the art will appreciate that various modifications to the procedures described herein can be made.

[0104] The invention provides a number of useful aminopyridinecyanamide compounds having various aminopyridine moieties such as aminopyridines (*e.g.*, 2-aminopyridines), aminoisoquinolines (*e.g.*, 1-aminoisoquinolines and 1-amino-6,7,8,9-tetrahydrobenzo[g]isoquinolines), aminofuopyridines (*e.g.*, 7-aminofuro[2,3-*c*]pyridines and 4-aminofuro[3,2-*c*]pyridines), and aminonaphthyridines (*e.g.*, 3-amino-1,7-naphthyridines and 8-amino-2,7-naphthyridines).

[0105] In one embodiment, the invention provides a compound according to Formula III:



or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is selected from C_{1-6} alkyl and C_{3-8} cycloalkyl;

5 R^{12a} and R^{12b} are independently selected from H, C_{1-6} alkyl, and C_{6-10} aryl, or

R^{12a} and R^{12b} are taken together to form C_{3-6} cycloalkyl, or

R^{12a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl which is optionally substituted with one or more R^{17} ;

each R^{13a} and each R^{13b} is independently selected from H, -OH, and C_{1-6} alkyl, or

10 one R^{13a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl,

or one R^{13b} and R^{12b} are taken together to form a 5- or 6-membered ring;

R^{14} is selected from H and halogen, or

R^{14} , R^{12a} , and R^{12b} are taken together to form a 6- to 8-membered ring, which is optionally substituted with one or more R^{18} , or

15 R^{14} and one R^{13a} are taken together to form a 5- to 8-membered ring, which is optionally substituted with one or more R^{18} , or

R^{14} is taken together with one R^{13a} and one R^{13b} on the same carbon atom to form a 5- to 8-membered ring, which is optionally substituted with one or more R^{18} , or

20 R^{14} , R^{11} , and R^{12a} are taken together to form a 6- to 10-membered bicyclic ring, which is optionally substituted with one or more R^{18} ,

R^{15a} and R^{15b} are independently selected from H and C_{1-6} alkyl;

R^{16} is independently selected from C_{1-6} alkyl and halogen;

each R^{17} is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-OH$, and $-N(R^{17a})_2$, wherein each R^{17a} is independently selected from H and C_{1-6} alkyl;

each R^{18} is independently selected from C_{1-6} alkyl and halogen;

5 Y is selected from O , S , $C(R^{19a})_2$, and NR^{19b} ;

each R^{19a} is selected from H and C_{1-6} alkyl, or

one R^{19a} and one R^{13b} on adjacent atoms are taken together to form a double bond;

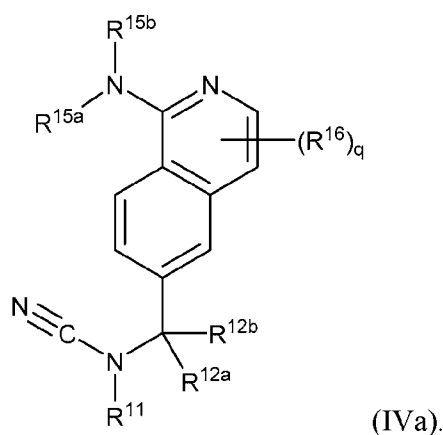
R^{19b} is selected from H and C_{1-6} alkyl, or

10 R^{19b} and R^{11} are taken together to form a 4- to 6-membered ring;

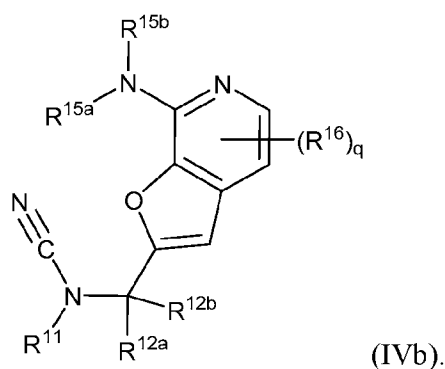
subscript m is 0, 1, 2, or 3; and

subscript q is 0 or 1.

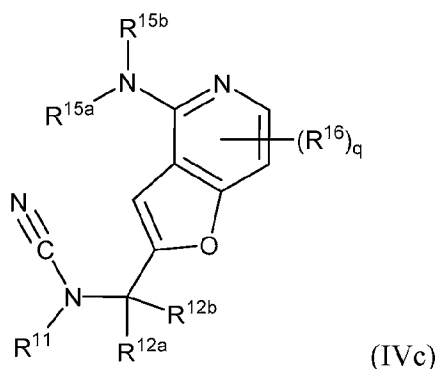
[0106] In some embodiments, the invention provides compounds according to Formula IVa:



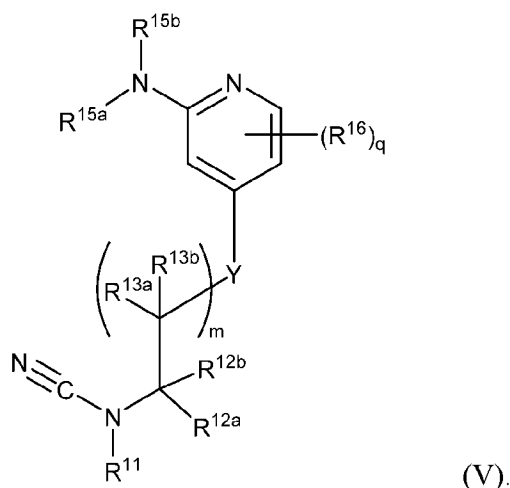
[0107] In some embodiments, the invention provides compounds according to Formula IVb:



[0108] In some embodiments, the invention provides compounds according to Formula IVc:



[0109] In some embodiments, the invention provides compounds according to Formula V:



5

[0110] In some embodiments, the invention provides compounds according to Formula III or Formula V wherein Y is O or S. In some embodiments, the invention provides compounds according to Formula III or Formula V wherein Y is CH₂. In some embodiments, W is selected from O, S, and CH₂, and each R^{13a} and each R^{13b} is selected from H and C₁₋₆ alkyl.

- 10 [0111] In some embodiments, Y is O and each R^{13a} and each R^{13b} is independently selected from H, -OH, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, Y is S and each R^{13a} and each R^{13b} is independently selected from H, -OH, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched
- 15 hexyl. In some embodiments, Y is CH₂ and each R^{13a} and each R^{13b} is independently selected from H, -OH, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl.

[0112] In some embodiments, Y is selected from O, S, and CH₂, and one of R^{13a} and R^{13b} is selected from H and –OH, and the remaining R^{13a} and R^{13b} groups are selected from H and C₁₋₆ alkyl.

[0113] In some embodiments, Y is CH(R^{19a}), and R^{19a} and one R^{13b} are taken together to form a double bond. In some embodiments, the grouping –CH(R^{19a})(CR^{13a}R^{13b})_m is selected from ethen-diyl, prop-1-en-1,3-diyl, and but-1-en-1,4-diyl.

[0114] In some embodiments, Y is CH(R^{19a}), subscript m is 1, and R^{19a} and R^{13b} are taken together to form a double bond. In some such embodiments, R^{13a} is selected from H, –OH, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl H. In some such embodiments, R¹³ is H.

[0115] In some embodiments, Y is NR^{19b}, and R^{19b} and R¹¹ are taken together to form a 5- or 6-membered ring. For example, R^{19b} and R¹¹ can form imidazolidin-diyl or piperazin-diyl. In some embodiments, R^{19b} and R¹¹ are taken together to form 1,4-piperazin-diyl.

[0116] In some embodiments, R^{12a} and R¹¹ are taken together to form 4- to 10-membered heterocyclyl in the compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, or Formula V. For example, R^{12a} and R¹¹ can be taken together to form aziridin-diyl, azetidin-diyl, diazetidin-diyl, pyrrolidin-diyl, imidazolidin-diyl, pyrazolidin-diyl, piperidin-diyl, piperazin-diyl, morpholin-diyl, azepan-diyl, diazepan-diyl, azocan-diyl, or indolin-diyl. In some embodiments, R^{12a} and R¹¹ are taken together to form azetidin-1,2-diyl, pyrrolidin-1,2-diyl, piperidin-1,2-diyl, indolin-1,2-diyl, or isoindolin-1,2-diyl.

[0117] In some embodiments, the compound has a structure according to Formula III, Formula IVa, Formula IVb, Formula IVc, or Formula V, and R^{12a} and R¹¹ are taken together to form pyrrolidin-1,2-diyl or piperidin-1,2-diyl. In some embodiments, the pyrrolidin-1,2-diyl or piperidin-1,2-diyl is substituted with one or two R¹⁷. In some embodiments, the pyrrolidin-1,2-diyl or piperidin-1,2-diyl is substituted with one R¹⁷. In some embodiments, R¹⁷ is selected from C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, –OH, and –N(R^{17a})₂. In some embodiments, R¹⁷ is selected from –OH, –NH₂, methoxy, and dimethylamino. [0118] In some embodiments, the compound has a structure according to Formula V, and R^{12a} and R¹¹ are taken together to form azetidin-1,2-diyl, pyrrolidin-1,2-diyl, piperidin-1,2-diyl, indolin-1,2-diyl, or isoindolin-1,2-diyl. In some embodiments, the azetidin-1,2-diyl, pyrrolidin-1,2-diyl, piperidin-1,2-diyl, indolin-1,2-diyl, or isoindolin-1,2-diyl is substituted with one or two R⁷. In some embodiments, the azetidin-1,2-diyl, pyrrolidin-1,2-diyl, piperidin-1,2-diyl, indolin-

1,2-diyl, or isoindolin-1,2-diyl is substituted with one R¹⁷. In some embodiments, R¹⁷ is C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -OH, or -N(R^{17a})₂. In some embodiments, R¹⁷ is selected from -OH, -NH₂, methoxy, and dimethylamino.

[0119] In some embodiments, the invention provides compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, and/or Formula V, wherein R^{12a} is H and R^{12b} is selected from H, C₁₋₆ alkyl, and C₆₋₁₀ aryl. For example, R^{12b} can be methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, or phenyl.

[0120] In some embodiments, the invention provides compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, and/or Formula V, wherein R¹¹ is C₁₋₆ alkyl. For example, R¹¹ can be methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, or branched hexyl. In some embodiments, R¹¹ is C₃₋₈ cycloalkyl. In some embodiments, R¹¹ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl. In some embodiments, the invention provides compounds of Formula III, Formula IVa, Formula IVb, Formula IVc, or Formula V as described above, wherein R¹¹ is selected from methyl, ethyl, isopropyl, cyclopentyl, and cyclohexyl. In some such embodiments, R¹¹ is selected from methyl, isopropyl, and cyclohexyl.

[0121] In some embodiments, the invention provides compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, and/or Formula V, wherein each of R^{15a} and R^{15b} is independently selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, R^{15a} is H and R^{15b} is selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, R^{15b} is selected from H, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl and R^{15a} is H. In some embodiments, R^{15a} and R^{15b} are H.

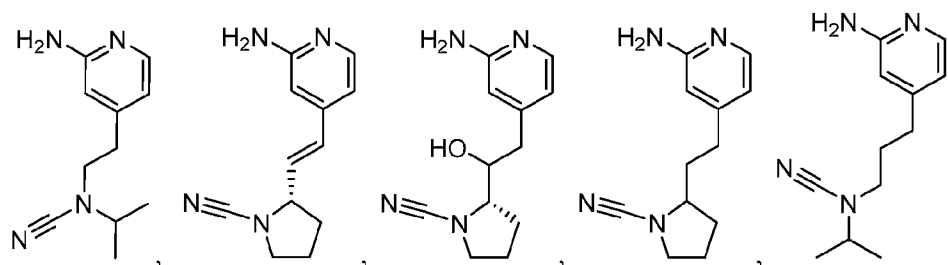
[0122] The aminopyridinecyanamide compounds of the invention can be prepared in protected form (*e.g.*, protected compounds wherein at least one of R^{15a}, R^{15b}, R^{17a}, and R^{19b} is an amine protecting group). A number of suitable protecting groups—as described, for example, by Green and Wuts (*Protective Groups in Organic Synthesis*, 4th Ed. 2007, Wiley-Interscience, New York)—can be used. In some embodiments, R^{15a} is H and R^{15b} is selected from benzyloxycarbonyl; 9-fluorenylmethyl-oxycarbonyl; *tert*-butyloxycarbonyl; and allyloxycarbonyl. In some embodiments, R^{15a} and R^{15b} are selected from benzyloxycarbonyl;

9-fluorenylmethyl-oxycarbonyl; *tert*-butoxycarbonyl; and allyloxycarbonyl. In some embodiments, R^{15a} is H and R^{15b} is *tert*-butoxycarbonyl. Compounds can also be prepared in alkylated form (*i.e.*, compounds wherein at least one of R^{15a}, R^{15b}, R^{17a}, and R^{19b} is an alkyl group). One or both of R^{17a} and R^{19b} can be, for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, or *t*-butyl.

[0123] In some embodiments, the invention provides compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, and/or Formula V, wherein subscript q is 0. In some embodiments, the invention provides compounds according to Formula III, Formula IVa, Formula IVb, Formula IVc, and/or Formula V, wherein subscript q is 1. In some such
 10 embodiments, subscript q is 1 and R¹⁶ is selected from fluoro, chloro, bromo, iodo, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, branched pentyl, *n*-hexyl, and branched hexyl. In some embodiments, subscript q is 1 and R¹⁶ is selected from fluoro, chloro, and methyl. In some embodiments, subscript q is 2.

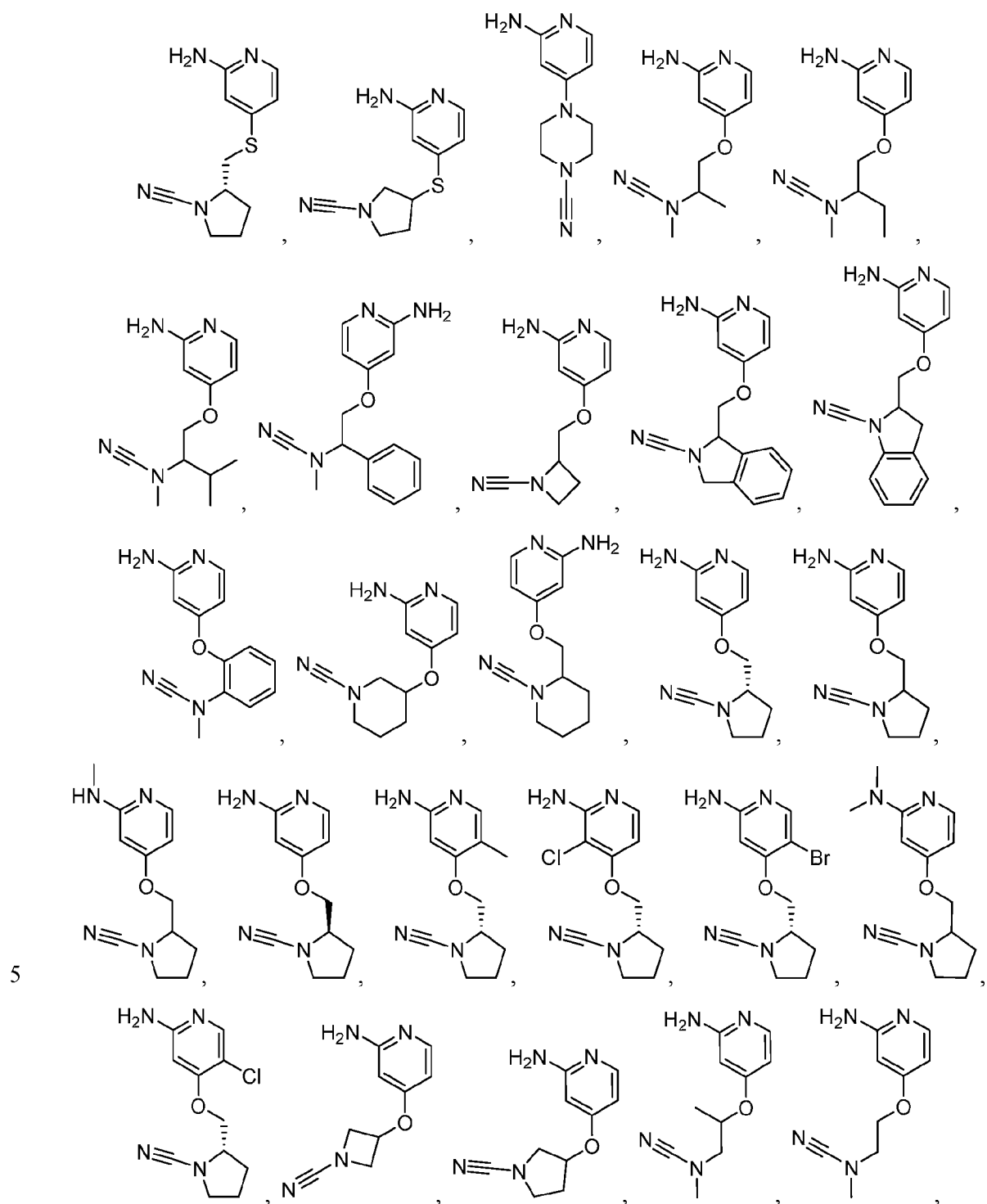
[0124] The compounds of the invention can be further substituted; a compound according
 15 to Formula III may contain, for example, an optionally substituted R¹¹ group, an optionally substituted R^{12a} and/or R^{12b} group, one or more optionally substituted R^{13a} and/or R^{13b} groups, an optionally substituted R¹⁴ group, an optionally substituted R^{15a} and/or R^{15b} group, one or more optionally substituted R¹⁶ groups, one or more optionally substituted R¹⁷ groups, one or more optionally substituted R¹⁸ groups, one or more optionally substituted R^{19a} groups,
 20 and/or an optionally substituted R^{19b} group.

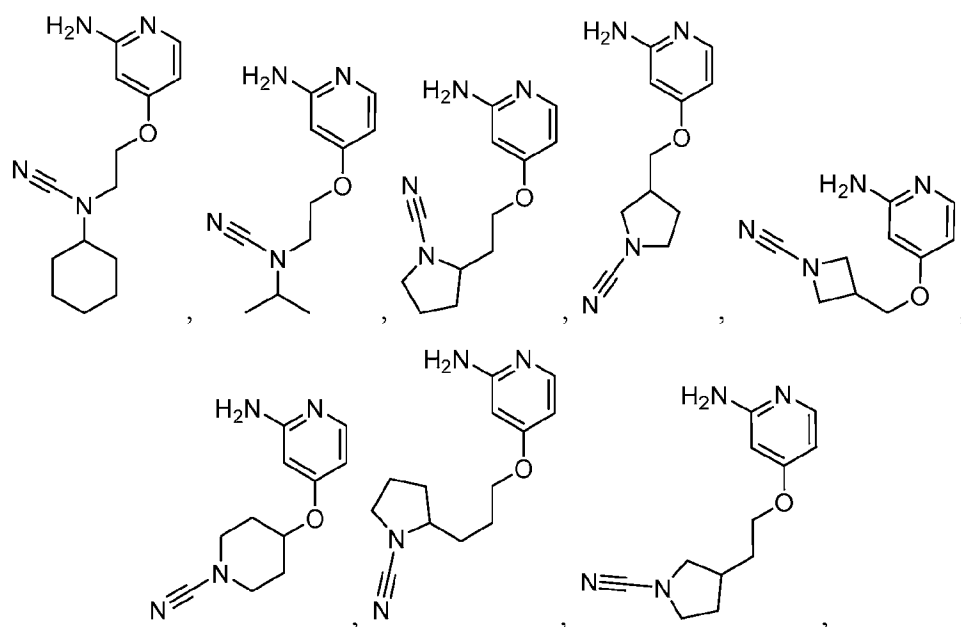
[0125] In some embodiments, the aminopyridinecyanamide compound is selected from:



and pharmaceutically acceptable salts thereof.

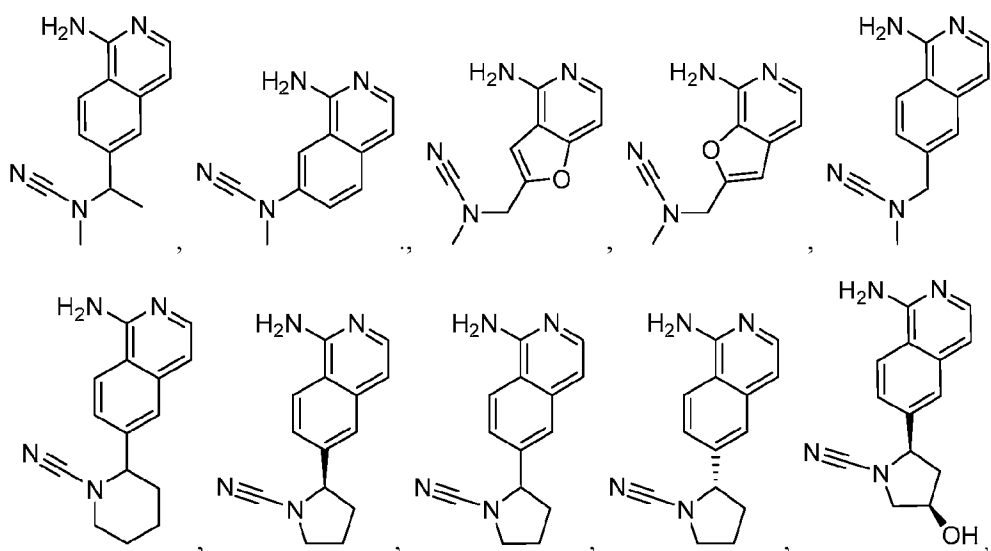
[0126] In some embodiments, the aminopyridinecyanamide compound is selected from:

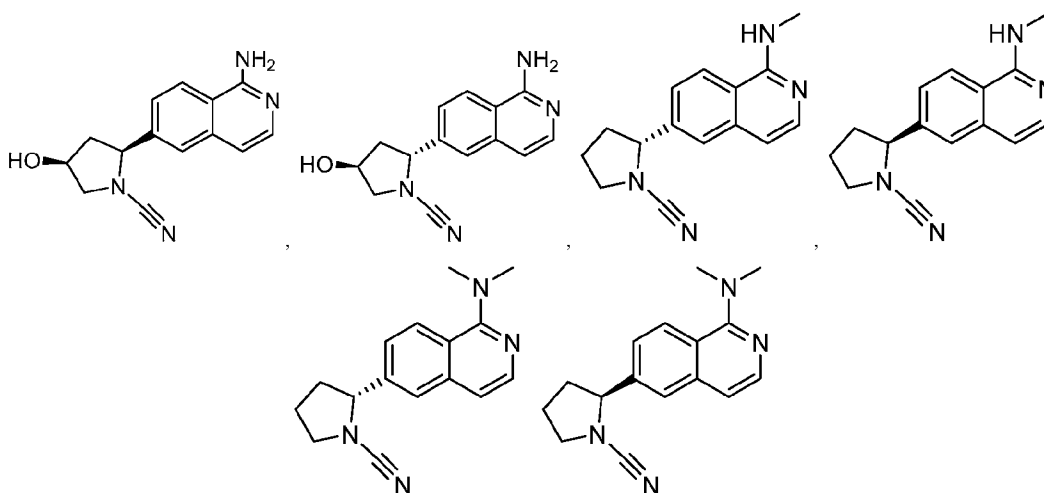




and pharmaceutically acceptable salts thereof.

[0127] In some embodiments, the aminopyridinecyanamide compound is selected from:



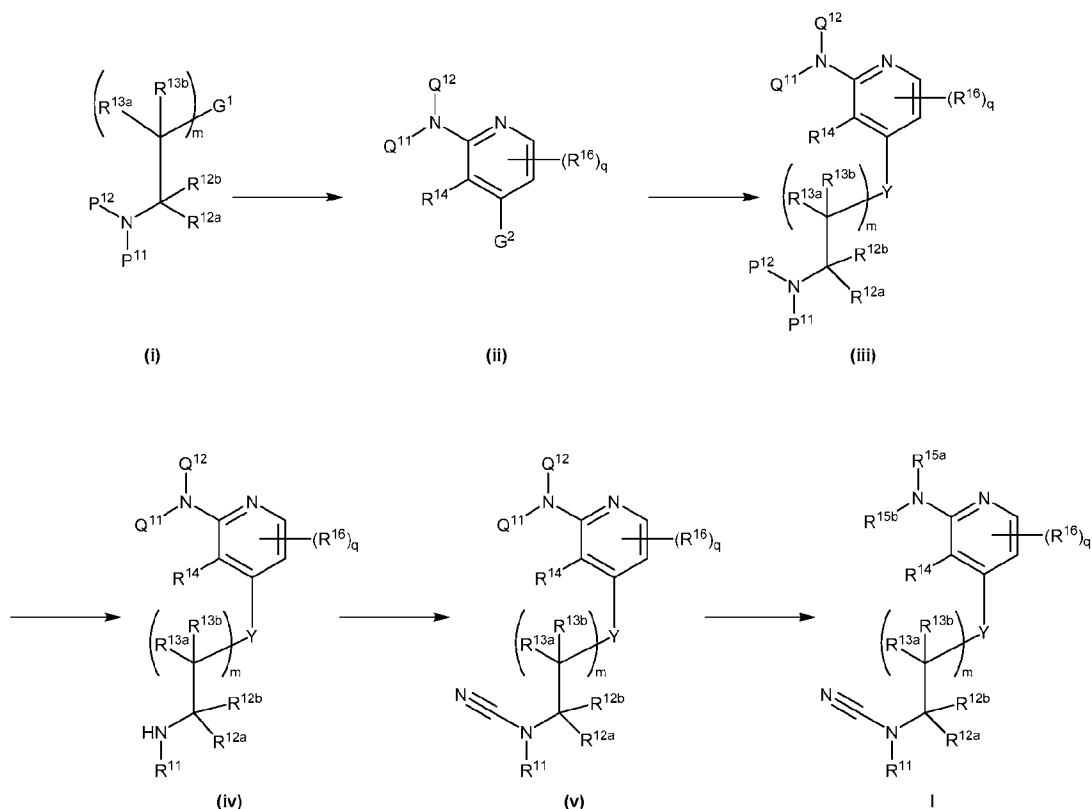


and pharmaceutically acceptable salts thereof.

[0128] The aminopyridinecyanamide compounds of the invention may be prepared by the approaches summarized in Scheme 2 and described below. As shown in Scheme 2, an amine (i), bearing a reactive group G^1 , can be reacted with an amino-heterocycle (ii), bearing a reactive group G^2 . This reaction involves transformation of reactive groups G^1 and G^2 to form intermediate (iii) containing a linkage Y between the amine and the amino-heterocycle structures. Prior to this reaction, the amine is usually protected and the amino-heterocycle is sometimes protected. In general, P^{11} is selected from R^{11} as described above, hydrogen, and a protecting group; P^{12} is selected from hydrogen and a protecting group; and Q^{11} and Q^{12} are independently selected from hydrogen, R^{15a} as described above, R^{15b} as described above, and a protecting group. Any suitable protecting group (*e.g.*, *tert*-butoxy carbonyl (Boc), benzyloxycarbonyl (Z), trifluoroacetyl, or another easily removed group) can be used for protecting the amine and the amino-heterocycle, and the protecting groups are typically chosen so that either may be removed without removing the other. For example, Boc may be removed by treatment with trifluoroacetic acid, which does not remove Z. Meanwhile, Z may be removed by hydrogenolysis in the presence of palladium on carbon, which does not remove Boc.

[0129] A wide variety of reactive groups G^1 and G^2 are suitable for forming the linkage Y between the amine and amino-heterocycle structures. A halide G^1 group or a sulfonate ester G^1 group can undergo a Williamson reaction with a phenol G^2 group or thiophenol G^2 group on the amino-heterocycle to form a linking ether or thioether. Employing a phosphine (*e.g.*, Ph_3P) and an azodicarboxylate (*e.g.*, DEAD) as co-reagents, an alcohol G^1 group can undergo a Mitsunobu reaction with a phenol G^2 group or thiophenol G^2 group to form a linking ether

Scheme 2



or thioether. An unprotected primary amine G¹ group or unprotected secondary amine G¹ group can undergo an Ullmann reaction with a halide G² group to form a secondary or tertiary linking amine. The Ullmann reaction can be catalyzed with a homogeneous copper or palladium catalyst, as described by Buchwald, Hartwig, Fu, and others.

[0130] An olefin G¹ group can undergo a Heck reaction with a halide G² group to form a linking olefin. An alkyne G¹ group can undergo a Sonagashira reaction with a halide G² group to form a linking alkyne. A boronic acid G¹ group can undergo a Suzuki reaction with a halide G² group or triflate G² group to form a biaryl linkage. A stannane G¹ group can undergo a Stille reaction with a halide G² group or triflate G² group to form a biaryl linkage. After a Heck, Sonagashira, Suzuki, or Stille reaction, certain intermediates (iii) (e.g., intermediates wherein P¹¹ and R^{12a} are taken together to form unsaturated heterocyclyl) can be hydrogenated to achieve partial or full saturation.

[0131] An aldehyde G¹ group on the amine may undergo a Grignard or “Grignard-like” reaction with an organomagnesium or organolithium G² group on the amino-heterocycle, to form a linkage bearing a secondary alcohol. A carboxylic acid G¹ group on the amine may

undergo a decarboxylating photoreaction with a halide G^2 group on the amino-heterocycle to form a carbon-carbon bond between the decarboxylated amine and the amino-heterocycle.

[0132] After the reaction involving reactive groups G^1 and G^2 , and formation of the linkage Y between the amine and amino-heterocycle, the protecting group on the amine can be removed to provide an amine (iv), and the amine can be reacted with cyanogen bromide to form a cyanamide (v). After formation of the cyanamide, any protecting group on the amino-heterocycle can be removed to provide products according to Formula III.

[0133] Other methods can also be used for preparing an amine (iv) for the corresponding cyanamide (v). In some instances, the amine precursor can be obtained via reductive amination of a ketone or aldehyde on the amino-heterocycle. In some instances, the amine precursor can be obtained via reduction of a nitro group on the amino-heterocycle and subsequent mono-alkylation of the resulting amino G^2 group. In some instances, the amine precursor can be obtained via reduction of a cyano group on the amino-heterocycle and subsequent monoalkylation of the resulting amino G^2 group. In some instances, the amine precursor can be obtained via simultaneous reduction of a nitro group and an olefin on the amino-heterocycle, and subsequent mono-alkylation of the resulting amino G^2 group. In some instances, the amine precursor can be obtained via simultaneous reduction of a cyano group and an olefin on the amino-heterocycle, and subsequent mono-alkylation of the resulting amino G^2 group. In some instances, the amine precursor can be obtained via a Schmidt reaction of a carboxylic acid on the amino-heterocycle, and subsequent mono-alkylation of the resulting amino G^2 group.

[0134] The compounds of the invention are highly active Rgp inhibitors, typically exhibiting Rgp IC_{50} values in the nanomolar and micromolar range.

[0135] The term " IC_{50} " indicates how much of a compound is needed to inhibit a given biological process (or component of a process, *e.g.*, an enzyme, cell, cell receptor, or microorganism) by one half (50%). The IC_{50} value for a particular test compound can be measured as follows. Fifty microliters (μ L) of an enzyme such as RgpA or RgpB (1 nM in 50 mM bis-Tris propane [pH 8.0] containing 1% [vol/vol] Triton X-100 and 5 mM 2-mercaptoethanol) is added to columns 1 to 11 of a 96-well plate, and 100 μ L is added to column 12. Two μ L of the test compound (100 μ L in 100% DMSO) is added to column 12, and the sample is mixed three times by pipetting. Then, a doubling dilution is prepared across the plate by serial transfer into adjacent wells. 50 μ L of Z-Arg-7-amido-4-

methylecoumarin ("Z-Arg-AMC;" 40 μ M in buffer) is added to all wells, and the contents are mixed. The reaction is monitored for AMC fluorescence for 15 min at 25°C, and the progress curves are automatically converted to rates by the Fluoroskan Ascent software. The IC₅₀ of a compound can then be determined by constructing a dose-response curve and examining the effect of different concentrations of the compound on reversing the activity of the enzyme. From the dose-response curve, IC₅₀ values can be calculated for a given compound by determining the concentration needed to inhibit half of the maximum biological response of the enzyme.

[0136] The method can also be used to assay enzymes including Kgp, trypsin, and cathepsin B. For Kgp, the substrate can be succinyl-Ala-Phe-Lys-AMC. For trypsin, the buffer can contain 10 mM Tris and 10 mM CaCl₂ (pH 8.0), and the substrate can be Z-Gly-Gly-Arg-AMC. For cathepsin B, the buffer can contain 50 mM sodium phosphate, 1 mM EDTA, and 10 mM 2-mercaptoethanol (pH 6.25), and the substrate can be Z-Arg-Arg-AMC.

[0137] In general, the Rgp IC₅₀ values for compounds of the invention range from about 0.01 nM to about 100 μ M. The Rgp IC₅₀ value for a compound of the invention can range, for example, from about 0.01 nM to about 0.1 nM, or from about 0.1 nM to about 1 nM, or from about 1 nM to about 100 nM, or from about 100 nM to about 250 nM, or from about 250 nM to about 500 nM, or from about 500 nM to about 750 nM, or from about 750 nM to about 1 μ M, or from about 1 μ M to about 10 μ M, or from about 10 μ M to about 25 μ M, or from about 25 μ M to about 50 μ M, or from about 50 μ M to about 75 μ M, or from about 75 μ M to about 100 μ M. The Rgp IC₅₀ value for a compound of the invention can range from about 0.01 nM to about 1 nM, or from about 0.05 nM to about 0.75 nM, or from about 0.1 nM to about 0.5 nM, from about 1 nM to about 100 nM, or from about 20 nM to about 80 nM, or from about 40 nM to about 60 nM, or from about 1 μ M to about 100 μ M, or from about 20 μ M to about 80 μ M, or from about 40 μ M to about 60 μ M.

[0138] In some embodiments, an Rgp inhibitor according to the invention has an RgpB IC₅₀ of 75 nM or less. In some embodiments, the Rgp inhibitor has an RgpB IC₅₀ of 50 nM or less. In some embodiments, the Rgp inhibitor has an RgpB IC₅₀ of 25 nM or less. In some embodiments, the Rgp inhibitor has an RgpB IC₅₀ of 10 nM or less. In some embodiments, the Rgp inhibitor has an RgpB IC₅₀ of 1 nM or less.

[0139] In certain embodiments, Rgp inhibitors according to the invention are selective for Rgp. As used herein, a "selective" Rgp inhibitor is a compound that does not substantially

affect the activity of proteases other than RgpA and RgpB when administered at a therapeutically effective dose for treating a disease or condition associated with *P. gingivalis* infection. Typically, a protease that is not substantially affected by a particular compound exhibits at least 90% of its normal enzymatic activity in the presence of the compound under physiological conditions. Selective Rgp inhibitors include those compounds that do not affect the activity of proteases other than Rgp when administered at a therapeutically effective dose for treating a brain disorder, periodontal disease, diabetes, a cardiovascular disease, arthritis, rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriatic arthritis, preterm birth, pneumonia, cancer, a kidney disease, a liver disease, a retinal disorder, or glaucoma associated with *P. gingivalis* infection. Preferably, selective Rgp inhibitors do not adversely affect the coagulation cascade when administered at therapeutically effective levels.

IV. Pharmaceutical Compositions and Administration of Gingipain Inhibitors

[0140] In a related embodiment, the invention provides a pharmaceutical composition comprising a compound of Formula I, Formula IIa, Formula IIb, Formula III, Formula IVa, Formula IVb, Formula IVc, or Formula V, and a pharmaceutically acceptable excipient. The pharmaceutical compositions can be prepared by any of the methods well known in the art of pharmacy and drug delivery. In general, methods of preparing the compositions include the step of bringing the active ingredient into association with a carrier containing one or more accessory ingredients. The pharmaceutical compositions are typically prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. The compositions can be conveniently prepared and/or packaged in unit dosage form.

[0141] Pharmaceutical compositions containing compounds of the invention can be formulated for oral use. Suitable compositions for oral administration include, but are not limited to, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs, solutions, buccal patches, oral gels, chewing gums, chewable tablets, effervescent powders, and effervescent tablets. Compositions for oral administration can be formulated according to any method known to those of skill in the art. Such compositions can contain one or more agents selected from

sweetening agents, flavoring agents, coloring agents, antioxidants, and preserving agents in order to provide pharmaceutically elegant and palatable preparations.

[0142] Tablets generally contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, including: inert diluents, such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as corn starch and alginic acid; binding agents, such as polyvinylpyrrolidone (PVP), cellulose, polyethylene glycol (PEG), starch, gelatin, and acacia; and lubricating agents such as magnesium stearate, stearic acid, and talc. The tablets can be uncoated or coated, enterically or otherwise, by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Tablets can also be coated with a semi-permeable membrane and optional polymeric osmogents according to known techniques to form osmotic pump compositions for controlled release.

[0143] Compositions for oral administration can be formulated as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (such as calcium carbonate, calcium phosphate, or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (such as peanut oil, liquid paraffin, or olive oil).

[0144] Rgp inhibitors can also be administered topically as a solution, ointment, cream, gel, or suspension, as well as in mouth washes, eye-drops, and the like. Still further, transdermal delivery of Rgp inhibitors can be accomplished by means of iontophoretic patches and the like.

[0145] Pharmaceutical compositions containing Rgp inhibitors can also be in the form of a sterile injectable aqueous or oleaginous solutions and suspensions. Sterile injectable preparations can be formulated using non-toxic parenterally-acceptable vehicles including water, Ringer's solution, and isotonic sodium chloride solution, and acceptable solvents such as 1,3-butane diol. In addition, sterile, fixed oils can be used as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic monoglycerides, diglycerides, or triglycerides.

[0146] In some embodiments, an Rgp inhibitor can be formulated with a polymer such as Pluronic F127 and delivered subcutaneously. Pluronic is a hydrogel that solidifies at body

temperature and can provide extended drug delivery over periods of time lasting from days to weeks.

[0147] Aqueous suspensions can contain one or more Rgp inhibitors in admixture with excipients including, but not limited to: suspending agents such as sodium
5 carboxymethylcellulose, methylcellulose, oleagino-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin, polyoxyethylene stearate, and polyethylene sorbitan monooleate; and preservatives such as ethyl, *n*-propyl, and *p*-hydroxybenzoate. Dispersible powders and granules (suitable for preparation of an aqueous suspension by the addition of water) can contain one or more
10 Rgp inhibitors in admixture with a dispersing agent, wetting agent, suspending agent, or combinations thereof. Oily suspensions can be formulated by suspending an Rgp inhibitor in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil), or in a mineral oil (*e.g.*, liquid paraffin). Oily suspensions can contain one or more thickening agents, for example beeswax, hard paraffin, or cetyl alcohol. These compositions can be preserved by the
15 addition of an anti-oxidant such as ascorbic acid.

[0148] The pharmaceutical compositions of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, such as gum acacia or gum tragacanth; naturally-occurring
20 phospholipids, such as soy lecithin; esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate; and condensation products of said partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate.

[0149] The use of hybrid molecules to promote active transport or nanoparticles can be used in certain embodiments to increase blood brain barrier transport. For example
25 liposomes, proteins, engineered peptide compounds or antibodies that bind to the receptors that transport proteins across the blood brain barrier including LPR-1 receptor, transferrin receptor, EGF-like growth factor or glutathione transporter can be used to increase penetration into the brain. Physical techniques including osmotic opening, ultrasound, lasers, sphenopalantine ganglion stimulation, direct intracranial, intrathecal, or intraventricular
30 delivery via a pump can be used.

[0150] Pharmaceutical compositions according to the invention can also include one or more additional active agents useful in the treatment of conditions associated with *P*.

gingivalis infection. In certain embodiments, the invention provides a pharmaceutical composition comprising one or more Rgp inhibitors as described herein in combination with one or more additional active agents for treatment of Alzheimer's disease. Several therapeutics are in development and in clinical use for treatment of Alzheimer's disease.

- 5 Therapeutic strategies include lowering circulating levels of β -amyloid and tau (as described in more detail below), stabilizing microtubules, removing atherosclerotic plaques, modulating autophagy, modulating neurotransmitter levels, and inhibiting GABA(A) $\alpha 5$ receptors. Such therapeutics can maintain and/or restore cognitive function in subjects with Alzheimer's disease; slow the decline of cognitive function; and promote neuroplasticity and recovery of
- 10 the brain.

- [0151] Active agents that can be combined with Rgp inhibitors in pharmaceutical compositions include, but are not limited to, antibiotics (*i.e.*, bacteriocidal compounds and bacteriostatic compounds), cholinesterase inhibitors, α -7 nicotinic receptor modulators, serotonin modulators, NMDA modulators, A β -targeted therapies, ApoE-targeted therapies,
- 15 microglia-targeted therapies, blood/brain barrier-targeted therapies, tau-targeted therapies, complement-targeted therapies, and anti-inflammatories.

- [0152] Any suitable antibiotic can be combined with one or more Rgp inhibitors in the pharmaceutical compositions of the invention. In certain embodiments, the invention provides a pharmaceutical composition containing one more Rgp inhibitors and an antibiotic
- 20 having a *P. gingivalis* MIC₅₀ of less than 25 μ g/ml. For example, the *P. gingivalis* MIC₅₀ of the antibiotic can be less than 20 μ g/ml, less than 15 μ g/ml, less than 10 μ g/ml, less than 8 μ g/ml, less than 6 μ g/ml, or less than 5 μ g/ml. In some embodiments, the *P. gingivalis* MIC₅₀ of the antibiotic is less than 1 μ g/ml. In some embodiments, the *P. gingivalis* MIC₅₀ of the antibiotic is less than 0.2 μ g/ml.

- 25 [0153] Examples of bacteriocidal and bacteriostatic compounds include, but are not limited to: quinolones (*e.g.*, moxifloxacin, gemifloxacin, ciprofloxacin, ofloxacin, trovafloxacin, sitafloxacin, and the like), β -lactams (*e.g.*, penicillins such as amoxicillin, amoxicillin-clavulanate, piperacillin-tazobactam, penicillin G, and the like; and cephalosporins such as ceftriaxone and the like), macrolides (*e.g.*, erythromycin, azithromycin, clarithromycin, and
- 30 the like), carbapenems (*e.g.*, doripenem, imipenem, meropenem, ertapenem, and the like), thiazolidines (*e.g.*, tizoxanidine, nitazoxanidine, RM 4807, RM 4809, and the like), tetracyclines (*e.g.*, tetracycline, minocycline, doxycycline, eravacycline, and the like),

clindamycin, metronidazole, and satranidazole. Bacteriocidal and bacteriostatic compounds also include agents that inhibit or otherwise interfere with formation of biofilms by anaerobic, gram-negative bacteria; such agents include oxantel, morantel, thiabendazole, and the like. Compositions of the invention can contain one or more Rgp inhibitors with one or more (e.g.,
5 two, three, four, five, six, or more) bacteriocidal/bacteriostatic compounds. Compositions containing bacteriocidal/bacteriostatic compounds can further contain a chlorhexidine (e.g., chlorhexidine digluconate) alone or in combination with a zinc compound (e.g., zinc acetate), can also be used in combination with the administered antibiotics.

[0154] In some embodiments, a combination of a penicillin (e.g., amoxicillin) and
10 metronidazole or a combination of penicillin (e.g., amoxicillin), metronidazole and a tetracycline is used. In some embodiments, the antibiotic is selected from minocycline, doxycycline, metronidazole, amoxicillin, clindamycin, augmentin, satranidazole, and combinations thereof.

[0155] Examples of suitable cholinesterase inhibitors include, but are not limited to,
15 donepezil, donepezil/memantine, galantamine, rivastigmine, and tacrine, as well as pharmaceutically acceptable salts thereof. Examples of suitable serotonin modulators include, but are not limited to, idalopirdine, RVT-101, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline, as well as pharmaceutically acceptable salts thereof. Examples of suitable alpha-7 nicotinic receptor modulators include, but are not limited to,
20 alpha-7 agonists such as encenicline and APN1125. Suitable NMDA modulators include, but are not limited to, NMDA receptor antagonists such as memantine and derivatives thereof.

[0156] Pharmaceutical compositions of the invention can also contain active agents that are directed to biomolecular targets associated with neurological diseases. Such targets include beta amyloid peptides (also referred to as beta amyloid, abeta, or A β), apolipoprotein E (also
25 referred to as ApoE), and microtubule-associated tau (also referred to as tau proteins, or simply as tau).

[0157] A β -targeted therapies include inhibitors of A β production (such as beta-secretase inhibitors, gamma-secretase inhibitors, alpha-secretase activators), inhibitors of A β aggregation, inhibitors of A β oligomerization, and up-regulators of A β clearance, among
30 others (see, e.g., Jia, *et al. BioMed Research International*, 2014. Article ID 837157, doi:10.1155/2014/837157). Examples of A β -targeted therapies include but are not limited to,

antibodies, pioglitazone, begacestat, atorvastatin, simvastatin, etazolate, and tramiprosate, as well as pharmaceutically acceptable salts thereof.

[0158] Examples of ApoE-targeted therapies include, but are not limited to retinoid X receptor agonists (*see*, Cramer, *et al.*, *Science* 2012. 335(6075): 1503–1506) and others described by Liu *et al.* (*Nat Rev Neurol.* 2013. 9(2): 106–118). Tau-targeted therapies include, but are not limited to, methylthioninium, leuco-methylthioninium, antibodies and those described by Lee, *et al.* (*Cold Spring Harb Perspect Med* 2011; 1:a006437).

[0159] Pharmaceutical compositions of the invention can also contain complement-targeted therapies. Such therapies target components of the complement system involved in the innate immune response. Complement targeted therapies include, but are not limited to, those described by Ricklin and Lambris (*Nat. Biotechnology* 2007. 25(11): 1265-1275).

[0160] Examples of suitable anti-inflammatories include, but are not limited to, NSAIDs such as apazone, diclofenac, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, piroxicam, and sulindac, as well as pharmaceutically acceptable salts thereof.

V. Methods for Inhibiting Gingipains and Treating Conditions Associated with *P. Gingivalis* Infection

[0161] In another embodiment, the invention provides a method of inhibiting a gingipain. The method includes contacting the gingipain with an effective amount of a compound as described herein. In certain embodiments, the gingipain is an arginine gingipain (*e.g.*, RgpA, RgpB, or a variant containing one or more amino acid substitutions, deletions, and/or other peptide sequence variations). Inhibiting the gingipain generally includes contacting the gingipain with an amount of the compound sufficient to reduce the activity of the gingipain as compared to the gingipain activity in the absence of the compound. For example, contacting the gingipain with the gingipain inhibitor can result in from about 1% to about 99% gingipain inhibition (*i.e.*, the activity of the inhibited gingipain ranges from 99% to 1% of the gingipain activity in the absence of the compound). The level of gingipain inhibition can range from about 1% to about 10%, or from about 10% to about 20%, or from about 20% to about 30%, or from about 30% to about 40%, or from about 40% to about 50%, or from about 50% to about 60%, or from about 60% to about 70%, or from about 70% to about 80%, or from about 80% to about 90%, or from about 90% to about 99%. The level of gingipain inhibition can range from about 5% to about 95%, or from about 10% to about 90%, or from

about 20% to about 80%, or from about 30% to about 70%, or from about 40% to about 60%. In some embodiments, contacting the gingipain with a compound as described herein will result in complete (*i.e.*, 100%) gingipain inhibition.

[0162] As described above, infection with *P. gingivalis* and gingipain activity have been
 5 linked to the development of periodontal disease, Alzheimer's and other brain disorders, cardiovascular disease, diabetes, cancer, liver disease, kidney disease, preterm birth, arthritis, pneumonia and other disorders. *See*: Bostanci, *et al.* FEMS Microbiol Lett, 2012. 333(1): 1-9; Ghizoni, *et al.* J Appl Oral Sci, 2012. 20(1): 104-12; Gatz, *et al.* Alzheimers Dement, 2006. 2(2): 110-7; Stein, *et al.* J Am Dent Assoc, 2007. 138(10): 1314-22; quiz 1381-2;
 10 Noble, *et al.* J Neurol Neurosurg Psychiatry, 2009. 80(11): 1206-11; Sparks Stein, *et al.* Alzheimers Dement, 2012. 8(3): 196-203; Velsko, *et al.* PLoS ONE, 2014. 9(5): e97811; Demmer, *et al.* J Dent Res, 2015. 94(9S): 201-S-11S; Atanasova and Yilmaz. Molecular Oral Microbiology, 2014. 29(2): 55-66; Yoneda, *et al.* BMC Gastroenterol, 2012. 12: 16.

[0163] Extracellular proteases produced by *P. gingivalis*, including Arginine Gingipain A (RgpA), Arginine Gingipain B (RgpB), and Lysine Gingipain (Kgp), can also degrade a
 15 broad range of proteins in connective tissue and plasma (*e.g.*, collagen, immunoglobulins, and proteinase inhibitors, etc.). Gingipains can enter systemic circulation and/or synoviocytes and chondrocytes, and they can also cause disruption to the kallikrein-kinin cascade, blood coagulation, and host defense systems. Patients with gingipains in their joints
 20 and circulatory system may be subject to gingipain-induced death of synovial cells and/or chondrocytes, contributing to osteoarthritis.

[0164] It has recently been discovered that RgpB and Kgp can infiltrate human and dog joints, contributing to the development of osteoarthritis. It is believed that *P. gingivalis* and gingipains can infiltrate joint tissues via a number of routes. Gingipains can be secreted,
 25 transported to outer membrane surfaces of *P. gingivalis*, or released in outer membrane vesicles by the bacterium. *P. gingivalis* has previously been identified in periodontal tissues, coronary arteries, aorta, and recently, the liver—release of *P. gingivalis* and/or gingipains from any of these niches into the systemic circulation could result in translocation of *P. gingivalis* and/or gingipains to the joints. *See*: Travis, *et al.* Adv Exp Med Biol, 2000. 477:
 30 455-65; Byrne, *et al.* Oral Microbiol Immunol, 2009. 24(6): 469-77; Mahendra, *et al.* J Maxillofac Oral Surg, 2009. 8(2): 108-13; Stelzel. Periodontol, 2002. 73(8): 868-70; Ishikawa, *et al.* Biochim Biophys Acta, 2013. 1832(12): 2035-2043.

[0165] *P. gingivalis* and/or gingipains may also enter joints by degrading the endothelial cells protecting the blood/joint barrier, or by a traumatic event to the joint, such as a meniscus injury, which permanently or transiently reduces the integrity of the joint tissues. Such a disruption in traumatic joint injury for example, may contribute to the infiltration of *P.*

5 *gingivalis* and/or gingipains in infected individuals and subsequent development of chronic osteoarthritis. People who are at a high risk of traumatic joint injury, including athletes in contact sports like football, could be preventatively treated with gingipain inhibitors to reduce the risk of trauma-related osteoarthritis.

[0166] *P. gingivalis* and gingipains may also reach the joint through other mechanisms
10 including active transport, passive transport or macrophage delivery. Osteoarthritis resulting from any of these mechanisms can be limited to a single joint or present in multiple joints.

[0167] Similar to humans, *P. gingivalis* infection and periodontal disease is one of the most common infectious diseases affecting adult dogs and cats. Dogs and cats with *P. gingivalis* infection and gingipains in their joints and circulatory system may experience periodontal
15 disease and osteoarthritis due to gingipain-induced cell death, which could be treated or prevented according to the methods of the invention. Aged dogs spontaneously develop many features of osteoarthritis, including a common inflammatory knee arthritis associated with degeneration of the anterior cruciate ligament (ACL). A study by Muir *et al.* of dogs with inflammatory knee arthritis and ACL degeneration detected DNA from a range of
20 bacterial species in 37% of knee joints from affected dogs. Muir *et al.* hypothesized that bacteria may be an important causative factor in the pathogenesis of inflammatory arthritis in dogs. In the Muir *et al.* study, DNA from *P. gingivalis* was not detected in the dog joints. See, Muir, *et al. Microb Pathog*, 2007. 42(2-3): 47-55. However, similar to humans, *P. gingivalis* is a common oral pathogen affecting adult dogs, and could potentially translocate
25 from the oral cavity to joint tissues as a result of bacteremia. *P. gingivalis* has been demonstrated to infect chondrocytes *in vitro* causing chondrocyte apoptosis, indicating a pathway for cartilage loss in osteoarthritis of both dogs and humans. See: Rohner, *et al. Calcif Tissue Int*, 2010. 87(4): p. 333-40; Houle, *et al. FEMS Microbiol Lett*, 2003. 221(2): p. 181-5; Kataoka, *et al. FASEB J*, 2014. 28: 3564-3578; Pischon, *et al. Ann Rheum Dis*, 2009.
30 68(12): p. 1902-7.

[0168] Rgp inhibitors can therefore be used to treat diseases and conditions, such as brain disorders, caused by or otherwise affected by *P. gingivalis*. Accordingly, another aspect of

the invention provides a method of treating a disease or condition associated with *P. gingivalis* infection. The method includes administering an effective amount of a compound or a composition of the invention, as described above, to a subject in need thereof.

[0169] In certain embodiments, compounds of the invention inhibit active Rgp in the brain of a mammal, *e.g.*, a human or an animal (*e.g.*, a dog), and are cytoprotective or neuroprotective. By “neuroprotective,” it is meant that the compounds prevent aberrant changes to neurons or death of neurons. Compounds of the invention are therefore useful, *e.g.*, in treatment of a brain disorder (*e.g.*, a neurodegenerative disease (*e.g.*, Alzheimer’s disease, Down’s syndrome, epilepsy, autism, Parkinson’s disease, essential tremor, fronto-temporal dementia, progressive supranuclear palsy, amyotrophic lateral sclerosis, Huntington’s disease, multiple sclerosis, mild cognitive impairment, age associated memory impairment, chronic traumatic encephalopathy, stroke, cerebrovascular disease, Lewy Body disease, multiple system atrophy, schizophrenia and depression, etc.), diabetes, cardiovascular disease, arthritis, rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriatic arthritis, retinal disorders (*e.g.*, age related macular degeneration) and glaucoma.

[0170] In some embodiments, the disease or condition is selected from a brain disorder, periodontal disease, diabetes, a cardiovascular disease, arthritis, rheumatoid arthritis, osteoarthritis, preterm birth, pneumonia, cancer, a kidney disease, a liver disease, a retinal disorder, and glaucoma.

[0171] In some embodiments, the disease or condition is a brain disorder.

[0172] In some embodiments, the brain disorder is selected from Alzheimer’s disease, Down’s syndrome, epilepsy, autism, Parkinson’s disease, essential tremor, fronto-temporal dementia, progressive supranuclear palsy, amyotrophic lateral sclerosis, Huntington’s disease, multiple sclerosis, mild cognitive impairment, age associated memory impairment, chronic traumatic encephalopathy, stroke, cerebrovascular disease, Lewy Body disease, multiple system atrophy, schizophrenia, and depression.

[0173] In some embodiments, the brain disorder is Alzheimer’s disease.

[0174] In some embodiments, the method further includes administering to the subject one or more active agents selected from a cholinesterase inhibitor, a serotonin modulator, an NMDA modulator, an A β targeted therapy, an ApoE targeted therapy, a microglia targeted

therapy, a blood brain barrier targeted therapy, a tau targeted therapy, a complement targeted therapy, and an anti-inflammatory.

[0175] In some embodiments, the disease or condition is periodontal disease. In some embodiments, the disease or condition is a liver disease. In some embodiments, the liver
5 disease is non-alcoholic steatohepatitis. In some embodiments, the disease or condition is a retinal disorder. In some embodiments, the retinal disorder is age-related macular degeneration.

[0176] In some embodiments, the disease or condition is cancer. In some embodiments, the cancer is breast cancer, oral cancer, pancreatic cancer, or glioblastoma multiforme.

10 [0177] Rgp inhibitors as described herein can be administered at any suitable dose in the methods of the invention. In general, an Rgp inhibitor is administered at a dose ranging from about 0.1 milligrams to about 1000 milligrams per kilogram of a subject's body weight (*i.e.*, about 0.1-1000 mg/kg). The dose of Rgp inhibitor can be, for example, about 0.1-1000
15 mg/kg, or about 1-500 mg/kg, or about 25-250 mg/kg, or about 50-100 mg/kg. The dose of Rgp inhibitor can be about 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 85, 90, 95, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000 mg/kg. The dosages can be varied depending upon the requirements of the patient, the severity of the disorder being treated, and the particular formulation being
20 administered. The dose administered to a patient should be sufficient to result in a beneficial therapeutic response in the patient. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of the drug in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the typical practitioner. The total dosage can be divided and administered in portions over a period of time suitable to treat to the disease or condition.

25 [0178] Rgp inhibitors can be administered for periods of time which will vary depending upon the nature of the particular disorder, its severity, and the overall condition of the subject to whom the Rgp inhibitor is administered. Administration can be conducted, for example, hourly, every 2 hours, three hours, four hours, six hours, eight hours, or twice daily including
30 every 12 hours, or any intervening interval thereof. Administration can be conducted once daily, or once every 36 hours or 48 hours, or once every month or several months. Following treatment, a subject can be monitored for changes in his or her condition and for alleviation of the symptoms of the disorder. The dosage of the Rgp inhibitor can either be increased in

the event the subject does not respond significantly to a particular dosage level, or the dose can be decreased if an alleviation of the symptoms of the disorder is observed, or if the disorder has been remedied, or if unacceptable side effects are seen with a particular dosage.

[0179] A therapeutically effective amount of an Rgp inhibitor can be administered to the subject in a treatment regimen comprising intervals of at least 1 hour, or 6 hours, or 12 hours, or 24 hours, or 36 hours, or 48 hours between dosages. Administration can be conducted at intervals of at least 72, 96, 120, 144, 168, 192, 216, or 240 hours (*i.e.*, 3, 4, 5, 6, 7, 8, 9, or 10 days). In certain embodiments, administration of one or more Rgp inhibitors is conducted in a chronic fashion over periods ranging from several months to several years. Accordingly, some embodiments of the invention provide a method of treating a disease or condition associated with *P. gingivalis* infection as described above, wherein the compound is administered to the subject for at least one year. In some embodiments, the compound is administered to the subject for at least 10 years. In some embodiments, the compound is administered to the subject for at least 60 years.

[0180] Administration of Rgp inhibitors according to the methods of the invention typically results in the reduction of circulating levels of active Rgp in a subject and/or the reduction of active Rgp in the brain. In certain embodiments, administration of an Rgp inhibitor according to the methods of the invention results in at least a 20% reduction of circulating levels of active Rgp and/or at least a 20% reduction of active Rgp in the brain. For example, the circulating levels of Rgp and/or the levels of Rgp in the brain are preferably reduced by from about 25% to about 95%, or from about 35% to about 95%, or from about 40% to about 85%, or from about 40% to about 80% as compared to the corresponding levels of Rgp 24 hours prior to the first administration of the Rgp inhibitor.

[0181] Rgp inhibitors can be administered alone or in combination with one or more additional therapeutically active agents, as described above. The one or more additional therapeutically effective agents include, *e.g.*,: (i) a pharmaceutically acceptable agent which inhibits RgpA, RgpB, and/or Kgp production, translocation of RgpA, RgpB, and/or Kgp into systemic circulation or brain, and/or pathological (*e.g.*, neurotoxic effects) of RgpA, RgpB, and/or Kgp in a mammal; (ii) an antibacterial agent which is bacteriostatic or bacteriocidal with respect to *P. gingivalis*; (iii) one or more antibodies which bind to RgpA, RgpB and/or Kgp (*e.g.*, 18E6, which binds to the first half of the immunoglobulin domain of RgpB; Kgp-specific monoclonal antibody, 7B9, which recognizes an epitope within the Kgp catalytic

domain; the RgpA antibody 61Bg 1.3, humanized versions of any of the foregoing, *etc.*); (iv) epitopes of antibodies which bind to RgpA, RgpB and/or Kgp or other proteins expressed by *P. gingivalis*; and (v) combinations of any of the foregoing.

[0182] The additional therapeutically active agents also include A β peptides level reducers, pathogenic level tau reducers, microtubule stabilizers, agents capable of removing atherosclerotic plaques, agents that lower circulating levels of β -amyloid and tau, modulators of autophagy, neurotransmitter level regulators, GABA(A) α 5 receptors inhibitors, and additional agents that help maintain and/or restore cognitive function and functional deficits of Alzheimer's disease, and/or slow down decline in cognitive functions and functional deficits in Alzheimer's disease.

[0183] Pharmaceutical compositions of the invention can contain one or more Rgp inhibitors as described herein in combination with ritonavir (RTV), which can increase bioavailability and increase blood brain barrier penetration. For example, ritonavir is commonly combined with oral peptidic HIV protease inhibitors to increase plasma levels by inhibiting the P450 3A4 enzyme and thus decreasing first-pass metabolism (*see*, Walmsley, *et al.*, *N Engl J Med*, 2002. 346(26): 2039-46). In addition, RTV binds to P-glycoprotein, a transmembrane efflux pump that is found in many tissues, including the blood brain barrier, allowing co-administered compounds better access to the brain (*see*, Marzolini, *et al.*, *Mol Pharm*, 2013. 10(6): 2340-9). Therefore, a combination of RTV and Rgp inhibitors can be used to increase plasma concentrations and brain levels of the gingipain inhibitors. As described in U.S. Pat. Appl. No. 14/875,416, oral administration of RTV 15 minutes prior to the Kgp inhibitor Kyt-36 increases the half-life therefore it is expected that RTV will also increase the half-life of other gingipain inhibitors.

[0184] In some embodiments, compounds of the invention can be administered with natural gingipain inhibitors including melabaricone C, isolated from nutmeg or polyphenolic compounds derived from plants, such as cranberry, green tea, apple, and hops can be administered in conjunction for treatment or prevention of brain disorders. Naturally and unnaturally occurring antimicrobial peptides including: κ -casein peptide (109–137) 34, histatin 5, and CL(14-25), CL(K25A) and CL(R24A, K25A), can also be administered in conjunction with the Rgp inhibitors of the invention. (*see, e.g.*, Taniguchi *et al.*, *Biopolymers*, 2014. 102(5): 379-89).

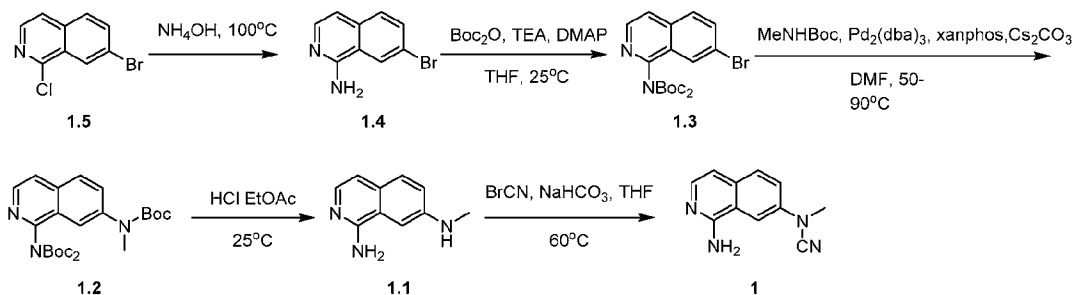
[0185] Rgp inhibitors as described herein can be administered with antibodies targeting gingipains or other *P. gingivalis* proteins. Antibodies may rely on damage to the blood brain barrier for access to the brain or peripheral interference with gingipains and *P. gingivalis* propagation. Antibodies can also help to stimulate the efficacy of the immune system in clearing the bacteria. New or existing antibodies to RgpA, RgpB, or Kgp can be utilized including 18E6 and 7B9. An RgpA antibody 61BG 1.3 has previously demonstrated efficacy topically in prevention of recolonization by *P. gingivalis* after periodontal treatment. See, Booth *et al.*, *Infect Immun*, 1996. 64(2): 422-7. Antibodies would preferably be humanized for use in humans. Methods known to those in the field for delivery of biologics to improve half-life and brain penetration can be used including, but not limited to, intravenous delivery, subcutaneous delivery, intranasal delivery, intrathecal delivery, intra-articular delivery, vector transport, and direct brain delivery.

[0186] The methods of the invention also encompass administration of Rgp inhibitors as described herein with one or more of the following additional therapeutically active agents or pharmaceutically acceptable salts thereof: an arginine derivative; histatin 5; baculovirus p35; a single point mutant of cowpox viral cytokine-response modifier (CrmA (Asp > Lys)); phenylalanyl-ureido-citrullinyl-valyl-cycloarginal (FA-70C1); (acycloxy)methyl ketone (Cbz-Phe-Lys-CH₂OCO-2,4,6-Me₃Ph); peptidyl chloro-methyl ketones (*e.g.*, chloromethyl ketone derivatives of arginine, chloromethyl ketone derivatives of lysine, and the like); fluoro-methyl ketones; bromo-methyl ketones; ketopeptides; 1-(3-phenylpropionyl)piperidine-3(R,S)-carboxylic acid [4-amino-1(S)-(benzothiazole-2-carbonyl)butyl]amide (A71561); azapeptide fumaramide; aza-peptide Michael acceptors; benzamidine compounds; acyclomethylketone; activated factor X inhibitors (*e.g.*, DX-9065a); cranberry nondialyzable fraction; cranberry polyphenol fraction; pancreatic trypsin inhibitor; Cbz-Phe-Lys-CH₂O-CO-2,4,6-Me₃-Ph; E-64; chlorhexidine; zinc (*e.g.*, zinc acetate); or a combination of two, three or more of any of foregoing. In some of these embodiments, Zn can enhance potency and selectivity of the compounds (*e.g.*, chlorhexidine, benzamidine, etc.) used in the methods of the invention.

[0187] An Rgp inhibitor of the invention can be administered in the same composition as an additional therapeutically active agent. Alternatively, the additional therapeutically active agent can be administered separately before, concurrently with, or after administration of the Rgp inhibitor.

VI. Examples

Example 1. Preparation of *N*-(1-aminoisoquinolin-7-yl)-*N*-methylcyanamide (1)



[0188] To a solution of compound **1.5** (3 g, 12.4 mmol, 1 *eq*) in NMP (30 mL) was added
 5 $\text{NH}_3\cdot\text{H}_2\text{O}$ (30 mL). The mixture was stirred 150°C for 15 hours. The reaction mixture was
 quenched by addition H_2O 100 mL at 25°C , and then extracted with EtOAc (100 mL x 3).
 The combined organic layers were washed with saturated brines (15 mL x 1), dried over
 anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude
 product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl
 10 acetate=1:1). Compound **1.4** (2.0 g, 9 mmol, 72.42% yield) was obtained as a brown oil.
 LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_9\text{H}_7\text{N}_2\text{Br}$:223; found 223; RT =1.049 min.

[0189] To a solution of compound **1.4** (1.90 g, 8.52 mmol, 1 *eq*) in THF (40 mL) was
 added TEA (3.45 g, 34.08 mmol, 4.73 mL, 4 *eq*) and Boc_2O (4.65 g, 21.30 mmol, 4.89 mL,
 2.50 *eq*) and DMAP (312.18 mg, 2.56 mmol, 0.30 *eq*). The mixture was stirred at 25°C for
 15 15 hours. The reaction mixture was quenched by addition H_2O 50 mL at 25°C and extracted
 with EtOAc (50mL x 3). The combined organic layers were washed with saturated brines (20
 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced
 pressure to give a crude product. The residue was purified by column chromatography (SiO_2 ,
 Petroleum ether/Ethyl acetate=2:1). Compound **1.3** (2.50 g, 5.91 mmol, 69.32% yield) was
 20 obtained as a yellow oil. ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.16 - 1.49 (m, 21 H) 7.89
 (d, J =5.77 Hz, 1 H) 7.92 - 8.03 (m, 2 H) 8.10 (s, 1 H) 8.42 (d, J =5.77 Hz, 1 H). LCMS (ESI):
 m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{BrO}_4$:423; found 423; RT =0.957 min.

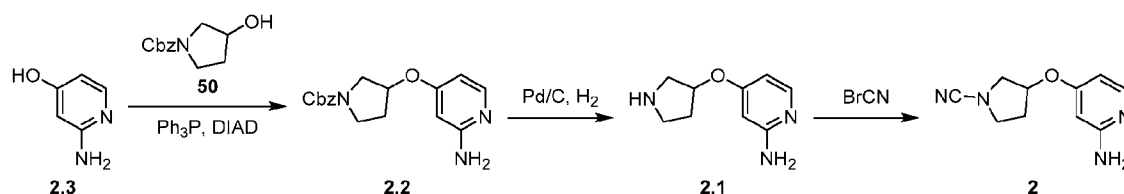
[0190] To a solution of compound **1.3** (1.50 g, 3.54 mmol, 1 *eq*) in DMF (30 mL) was
 added tert-butyl *N*-methylcarbamate (557.21 mg, 4.25 mmol, 1.20 *eq*), Cs_2CO_3 (3.46 g, 10.62
 25 mmol, 3 *eq*), 4, 5-BIS (DIPHENYLPHOSPHINO)-9, 9-DIMETHYLYXANTHENE (819.33
 mg, 1.42 mmol, 0.40 *eq*) and $\text{Pd}_2(\text{dba})_3$ (972.49 mg, 1.06 mmol, 0.30 *eq*). The mixture was
 stirred at 80°C for 2 hours. The reaction mixture was quenched by addition H_2O 50 mL at

25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (15 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 10:1). Compound **1.2** (1.20 g, 2.53 mmol, 71.58% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] calcd for C₂₅H₃₅N₃O₆: 474; found 474; RT=0.936 min.

[0191] A mixture of compound **1.2** (1.20 g, 2.53 mmol, 1 eq) in HCl/EtOAc (10 mL) was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give compound **1.1** (600 mg, 2.12 mmol, 83.92% yield, 3HCl) was obtained as a yellow solid. ¹H NMR (400 MHz, DEUTERIUM OXIDE) δ ppm 7.08 (d, *J*=7.06 Hz, 1 H) 7.38 (d, *J*=6.84 Hz, 1 H) 7.59 - 7.69 (m, 2 H) 7.78 (d, *J*=8.60 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₁N₃O₆: 174; found 174; RT=0.236 min.

[0192] To a solution of compound **1.1** (100 mg, 406.27 μmol, 1 eq, 2HCl) in DMSO (3 mL) was added NaHCO₃ (170.65 mg, 2.03 mmol, 79.01 μL, 5 eq) and BrCN (43.03 mg, 406.27 μmol, 29.88 μL, 1 eq). The mixture was stirred at 60 °C for 0.5 hour. The residue was purified by prep-HPLC (neutral condition). Product **1** (2 mg, 8.07 μmol, 1.99% yield, 80% purity) was obtained as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.43 - 3.48 (m, 3 H) 6.78 - 6.84 (m, 2 H) 6.88 - 6.96 (m, 1 H) 6.89 - 6.92 (m, 1 H) 7.51 - 7.55 (m, 1 H) 7.71 (d, *J*=2.43 Hz, 1 H) 7.75 (d, *J*=5.73 Hz, 1 H) 7.79 (d, *J*=8.82 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₀N₄: 199; found 199; RT=2.246 min.

Example 2. Preparation of 3-((2-aminopyridin-4-yl)oxy)pyrrolidine-1-carbonitrile (**2**)



[0193] To a solution of compound **2.3** (800 mg, 7.27 mmol, 1 eq) in DCM (30 mL) was added compound **50** (1.61 g, 7.27 mmol, 1 eq), PPh₃ (2.86 g, 10.91 mmol, 1.50 eq) and DIAD (2.21 g, 10.91 mmol, 2.12 mL, 1.50 eq) in turn at 0°C under N₂. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water 20 mL, extracted with EtOAc (20mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1).

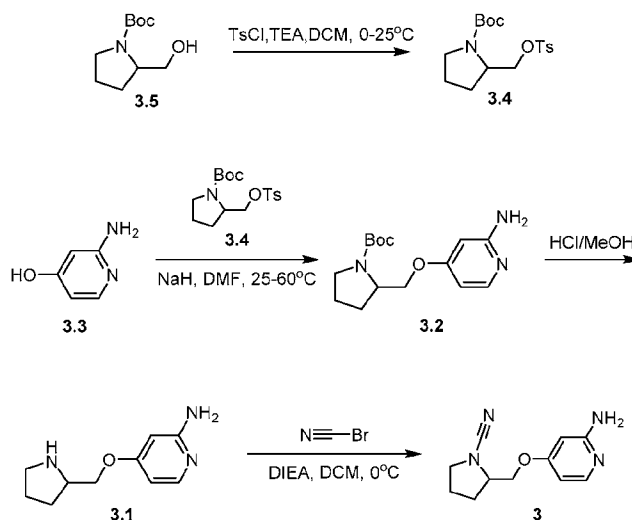
Compound **2.2** (750 mg, 2.39 mmol, 32.92% yield) was obtained as a white solid. ¹H NMR (400 MHz, chloroform-d) ppm 2.09 - 2.20 (m, 2 H) 3.51 - 3.74 (m, 4 H) 4.45 (s, 2 H) 4.90 (s, 1 H) 5.93 (s, 1 H) 6.21 (d, J=6.0 Hz, 1 H) 7.33 - 7.37 (m, 5 H) 7.91 (d, J=6.4 Hz, 1 H).

[0194] H₂ was bubbled into a solution of compound **2.2** (400 mg, 1.28 mmol, 1 *eq*) and Pd/C (40 mg) in MeOH (40 mL) at 25°C under 50 psi for 16 hours. The reaction mixture was filtered, the filter was concentrated under reduced pressure to remove solvent. Compound **2.1** (200 mg, 1.12 mmol, 87.18% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, methanol-d₄) ppm 1.93 - 1.97 (m, 2 H) 2.09 - 2.12 (m, 2 H) 2.88 - 3.09 (m, 4 H) 4.90 - 4.93 (m, 1 H) 6.06 (d, J=2.0 Hz, 1 H) 6.20 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.69 (d, J=6.4 Hz, 1 H).
LCMS (ESI): m/z: [M + H] calcd for C₈H₁₁N₃O·2(C₂H₅F₃O₂):166; found 166; RT=0.214 min.

[0195] To a solution of compound **2.1** (100 mg, 557.97 μmol, 1 *eq*) in THF (5 mL) was added DIEA (144.22 mg, 1.12 mmol, 194.89 μL, 2 *eq*) and BrCN (59.10 mg, 557.97 μmol, 41.04 μL, 1 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 0°C for 2 hours.
The reaction mixture was added water 10 mL, extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by p-TLC (SiO₂, Ethyl acetate = 0:1). Product **2** (9 mg, 44.07 μmol, 7.90% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₂N₄O:204; found 205; RT=1.672 min. ¹H NMR (400 MHz, chloroform-d) ppm 2.12 - 2.26 (m, 2 H) 3.59 - 3.69 (m, 4 H) 4.44 (s, 2 H) 4.92 (s, 1 H) 5.92 (d, J=2.0 Hz, 1 H) 6.20 (dd, J=6.4 Hz, 2.0 Hz, 1 H) 7.93 (d, J=6.0 Hz, 1 H)

Example 3. Preparation of 2-(((2-aminopyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (3)

[0196] To a mixture of compound **3.5** (700 mg, 3.48 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (796.15 mg, 4.18 mmol, 1.20 *eq*) in DCM (15 mL) was added DMAP (68.02 mg, 556.80 μmol, 0.16 *eq*) and TEA (528.21 mg, 5.22 mmol, 723.58 μL, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was then heated to 25 °C and stirred for 10 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **3.4**



(1.30 g, crude) as a colorless oil. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{17}H_{25}NSO_5$: 355; found 300; RT=0.866 min.

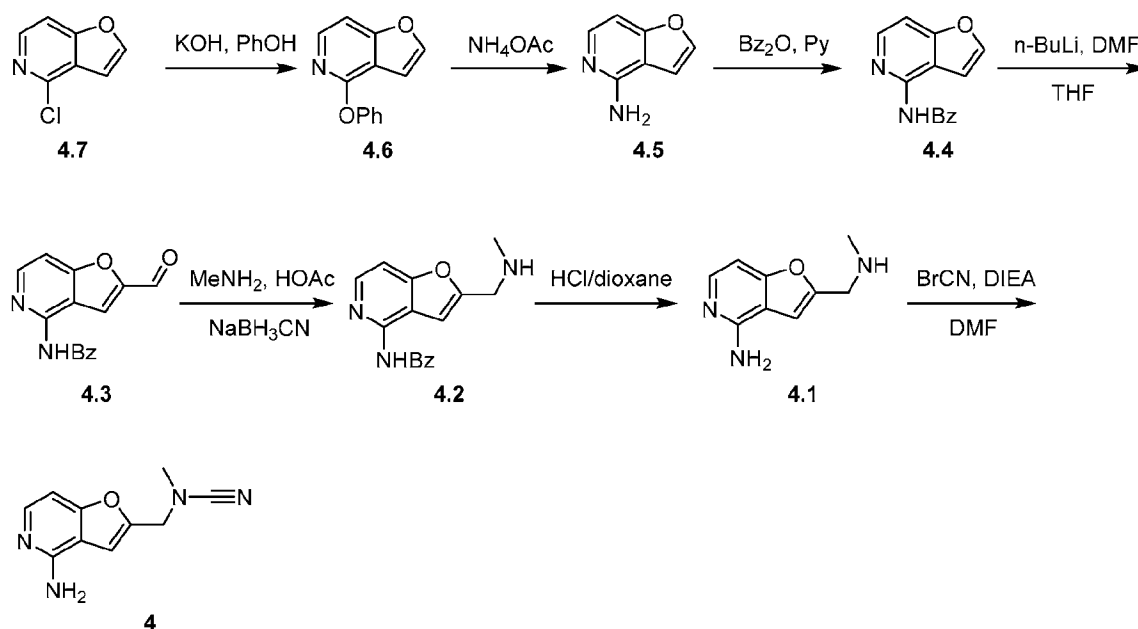
[0197] To a solution of compound **3.3** (443.30 mg, 4.03 mmol, 1.10 *eq*) in DMF (20 mL) was added NaH (131.76 mg, 5.49 mmol, 1.50 *eq*) portionwise at 25 °C under N_2 . The mixture was stirred at 25 °C for 30 mins, then was added compound **3.4** (1.30 g, 3.66 mmol, 1 *eq*). The mixture was heated to 60 °C and stirred for 9.5 hours. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), 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=20:1) to give compound **3.2** (200 mg, 681.76 μ mol, 18.63% yield) as a colorless oil. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{15}H_{23}N_3O_3$: 293; found 294; RT=0.663 min.

[0198] Compound **3.2** (200 mg, 681.76 μ mol, 1 *eq*) was added into a solution of HCl/MeOH (5 mL). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was concentrated under reduced pressure to give compound **3.1** (220 mg, crude) as a yellow solid. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{10}H_{15}N_3O$: 193; found 194; RT=0.161 min.

[0199] To a mixture of compound **3.1** (100 mg, 517.46 μ mol, 1 *eq*) and DIEA (267.51 mg, 2.07 mmol, 361.50 μ L, 4 *eq*) in DCM (2 mL) was added carbononitridic bromide (54.81 mg, 517.46 μ mol, 38.06 μ L, 1 *eq*) in one portion at 0 °C under N_2 . The mixture was stirred at 0 °C for 30 mins. The reaction mixture diluted with H_2O 3 mL and extracted with DCM 9 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried over

Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **3** (40 mg, 183.28 μmol, 35.42% yield) as a yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O: 218; found 219; RT=1.884 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.83 - 1.93 (m, 1 H) 1.93 - 2.05 (m, 2 H) 2.07 - 2.18 (m, 1 H) 3.38 - 3.58 (m, 2 H) 3.89 - 4.06 (m, 3 H) 4.46 (br s, 2 H) 6 (d, *J*=2.01 Hz, 1 H) 6.25 (dd, *J*=6.02, 2.01 Hz, 1 H) 7.90 (d, *J*=5.52 Hz, 1 H).

Example 4. Preparation of *N*-((4-aminofuro[3,2-*c*]pyridin-2-yl)methyl)-*N*-methylcyanamide (4**)**



10

[0200] To a solution of compound **4.7** (500 mg, 3.26 mmol, 1 *eq*) in PhOH (2.45 g, 26.05 mmol, 2.29 mL, 8 *eq*) was added KOH (365.37 mg, 6.51 mmol, 2 *eq*) at 25°C under N₂. The resulting mixture was stirred at 140°C for 16 hrs. TLC (PE:EtOAc = 5:1, R_f = 0.49) showed the reaction was successful. The reaction mixture was added water (10 mL), extracted with EtOAc (15 mL x 3). The organic phase was separated, washed with saturated NaCl (15 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue of compound **4.6** (0.5 g, crude) as a yellow oil which was combined with a second batch for a total of 1.5 g.

[0201] To a mixture of compound **4.6** (1.5 g, 7.10 mmol, 1 *eq*) in NH₄OAc (12.50 g, 162.20 mmol, 22.84 *eq*) in one portion under N₂. The mixture was stirred at 140 °C for 12 hours, then heated to 180 °C and stirred for 12 hours. The mixture was allowed to cool to

ambient temperature, after which 3 N sodium hydroxide (20 ml) was added with stirring. The thus obtained solution was extracted with ethyl acetate (2 x 10 ml) and the combined organic layers were extracted with 2 N hydrochloric acid (20 ml). Subsequently, the pH of the aqueous layer was adjusted to 12 with 2 N sodium hydroxide. Extraction with ethyl acetate (20 ml) then afforded an organic layer, which was washed with brine (10 ml), dried and concentrated under reduced pressure to give compound **4.5** (900 mg, 6.71 mmol, 94.48% yield) was obtained as light yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₇H₆N₂O:135; found 135; RT=0.199 min.

[0202] To a mixture of compound **4.5** (900 mg, 6.71 mmol, 1 eq) and benzoyl benzoate (3.04 g, 13.42 mmol, 2.53 mL, 2 eq) in Py (10 mL) in one portion under N₂. The mixture was stirred at 150 °C for 8 hours. The mixture was poured into 500 mL of water. The resulting precipitated was filtered off, washed with water, and dried to afford crude product of compound **4.4** (1.5 g, 6.30 mmol, 93.84% yield) was obtained as white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₄H₁₀N₂O₂:239; found 239; RT=1.582 min.

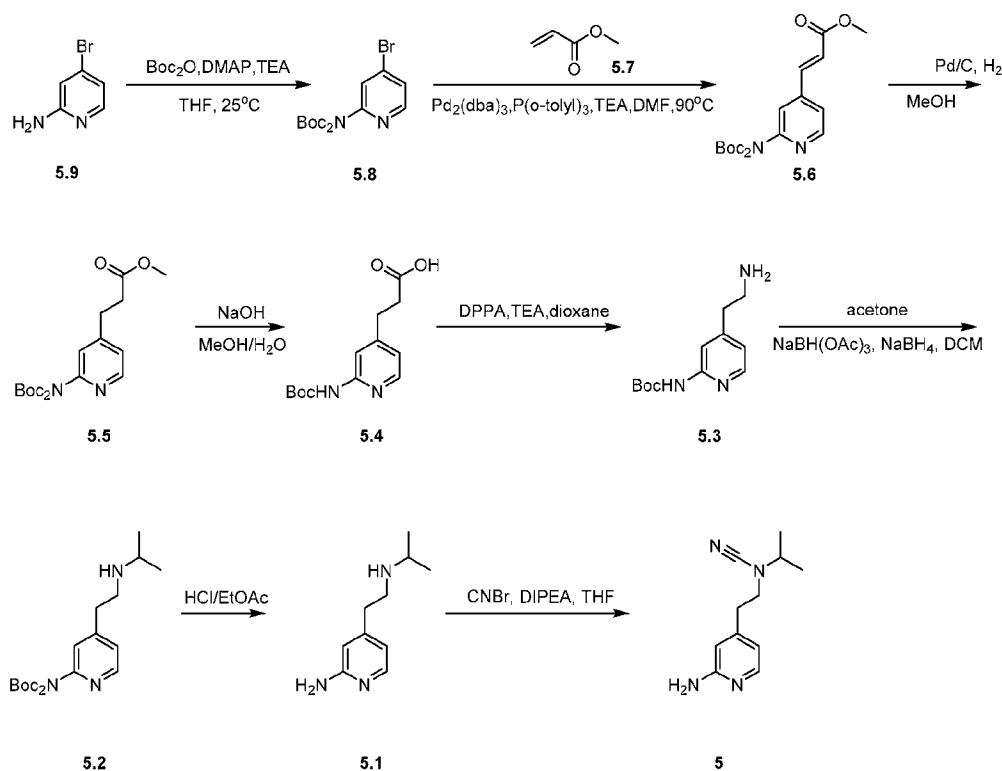
[0203] To a mixture of compound **4.4** (500 mg, 2.10 mmol, 1 eq) in THF (3 mL) was added n-BuLi (2.5 M, 2.10 mL, 2.5 eq) in one portion at -78 °C under N₂. The mixture was stirred at -78 °C for 1h, then was added DMF (613.58 mg, 8.39 mmol, 645.87 µL, 4 eq) dropwise and stirred at -78 °C for 1h. TLC (PE: EtOAc = 3:1, R_f = 0.4) showed the reaction was successful. The reaction mixture was quenched by addition H₂O (20 mL), and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product of compound **4.3** (0.24 g, crude) as white solid.

[0204] To a mixture of compound **4.3** (200 mg, 751.17 µmol, 1 eq) in MeNH₂ (116.65 mg, 3.76 mmol, 5 eq) stirred at 25 °C for 1h, was added NaBH₃CN (188.82 mg, 3 mmol, 4 eq) then was added AcOH (67.66 mg, 1.13 mmol, 64.44 µL, 1.5 eq) until pH=0.3. The mixture was stirred at 25 °C for 11 hr. TLC (PE: EtOAc = 1:1, R_f = 0.3) showed the reaction was successful. The reaction residue was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL x 3). The aqueous layer added 5N aq.NaOH until PH=11 and extracted with EtOAc (20 mL x 4). The combined organic layers were washed with brine 20 mL (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue of compound **4.2** (100 mg, crude) was obtained as white solid.

[0205] To a mixture of compound **4.2** (100 mg, 355.48 μ mol, 1 *eq*) in dioxane (0.5 mL) was added HCl (0.5 mL) in one portion at 80°C under N₂. The mixture was stirred at 80°C for 2 hours. The reaction solution was concentrated in vacuum to obtain compound **4.1** (100 mg, crude) as black brown solid. LCMS (ESI): *m/z*: [M + H] calcd for C₉H₁₁N₃O:178; found:178; RT=0.162 min.

[0206] To a mixture of compound **4.1** (100 mg, 399.80 μ mol, 1 *eq*, 2HCl) in DMF (2 mL) was added DIPEA (206.69 mg, 1.60 mmol, 278.55 μ L, 4 *eq*) in one portion at 25°C under N₂. Then BrCN (46.58 mg, 439.78 μ mol, 32.35 μ L, 1.1 *eq*) added at 0 °C and stirred at 0 °C for 20 min. The residue was purified by prep- HPLC (neutral condition) to give product **4** (1.95 mg, 9.64 μ mol, 2.41% yield) was obtained as light yellow oil. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 7.76 (d, *J*=6.11 Hz, 1 H) 6.97 (s, 1 H) 6.83 (dd, *J*=6.11, 0.85 Hz, 1 H) 4.36 (s, 2 H) 2.92 (s, 3 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₀H₁₀N₄O:203; found 203; RT=1.683 min.

Example 5. Preparation of *N*-(2-(2-aminopyridin-4-yl)ethyl)-*N*-isopropylcyanamide (**5**)



[0207] To a solution of compound **5.9** (20 g, 115.60 mmol, 1 *eq*) in THF (400 mL) was added Boc₂O (63.07 g, 289 mmol, 66.39 mL, 2.50 *eq*), DMAP (4.24 g, 34.68 mmol, 0.30 *eq*) and TEA (35.09 g, 346.80 mmol, 48.07 mL, 3 *eq*) at 25°C under N₂. The resulting mixture

was stirred for 16 hours. The reaction mixture was added water 100 mL, extracted with EtOAc (300 mL x 3). The organic phase was separated, washed with NH₄Cl 100 mL and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 5:1).

5 Compound **5.8** (27.70 g, 74.21 mmol, 64.20% yield) was obtained as a colorless oil.

[0208] To a solution of compound **5.8** (27.70 g, 74.21 mmol, 1 *eq*) in DMF (460 mL) was added TEA (15.02 g, 148.43 mmol, 20.57 mL, 2 *eq*), P(o-tolyl)₃ (6.78 g, 22.26 mmol, 0.30 *eq*), Pd₂(dba)₃ (6.80 g, 7.42 mmol, 0.10 *eq*) and methyl prop-2-enoate **5.7** (25.56 g, 296.86 mmol, 26.62 mL, 4 *eq*) in turn at 25°C under N₂. The resulting mixture was stirred at 80°C
10 for 13 hours. The reaction mixture was added H₂O 500 mL at 25°C, extracted with EtOAc (500 mL x 3). The combined organic layers were washed with saturated brine 200 mL (200 mL x 1), dried over dry Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=50:1 to 10:1). Compound **5.6** (24 g, 63.42 mmol, 85.46% yield) was obtained as a
15 white solid.

[0209] To a solution of compound **5.6** (24 g, 63.42 mmol, 1 *eq*) in MeOH (1.50 L) was added Pd-C under Ar₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 24 hours. Pd/C was filtered off by filtration. The filtrate was concentrated to dry. Compound **5.5** (22 g, 57.83
20 mmol, 91.19% yield) was obtained as a white solid.

[0210] To a mixture of compound **5.5** (6 g, 15.77 mmol, 1 *eq*) in MeOH (60 mL) was added NaOH (1.89 g, 47.31 mmol, 3 *eq*) in one portion at 25°C. The mixture was stirred at 25°C for 17h. The pH was adjusted to around 4 by progressively adding citric acid. Then the solid was precipitate out, filtered to give compound **5.4** (4 g, 10.92 mmol, 69.22% yield) as a
25 white solid. LCMS (ESI): m/z: [M - H] calcd for C₁₃H₁₈N₂O₄: 266; found 265; RT=0.859 min. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.45 - 1.59 (m, 7 H) 2.56 - 2.70 (m, 2 H) 2.83 - 2.98 (m, 2 H) 6.91 (dd, *J*=5.18, 1.43 Hz, 1 H) 7.71 (d, *J*=0.66 Hz, 1 H) 8.06 (d, *J*=5.07 Hz, 1 H).

[0211] To a mixture of compound **5.4** (2 g, 7.51 mmol, 1 *eq*) and DPPA (2.48 g, 9.01
30 mmol, 1.95 mL, 1.20 *eq*) in dioxane (20 mL) was added TEA (1.52 g, 15.02 mmol, 2.08 mL, 2 *eq*) in one portion at 25°C under N₂. The mixture was stirred at 25 °C for 10 min, then heated to 90 °C and stirred for 2 hours. Then the mixture was added dropwise into a solution

of NaOH (1.20 g, 30.04 mmol, 4 *eq*) and stirred for 18 hours at 25°C. The pH was adjusted to around 6 by progressively adding 1M HCl, then the mixture was partitioned between EtOAc (30) and water (30). The combined organic layers were washed with brine 30 mL (30 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **5.3** (800 mg, 3.37 mmol, 44.89% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₂H₁₉N₃O₂: 237; found 294; RT=1.547 min.

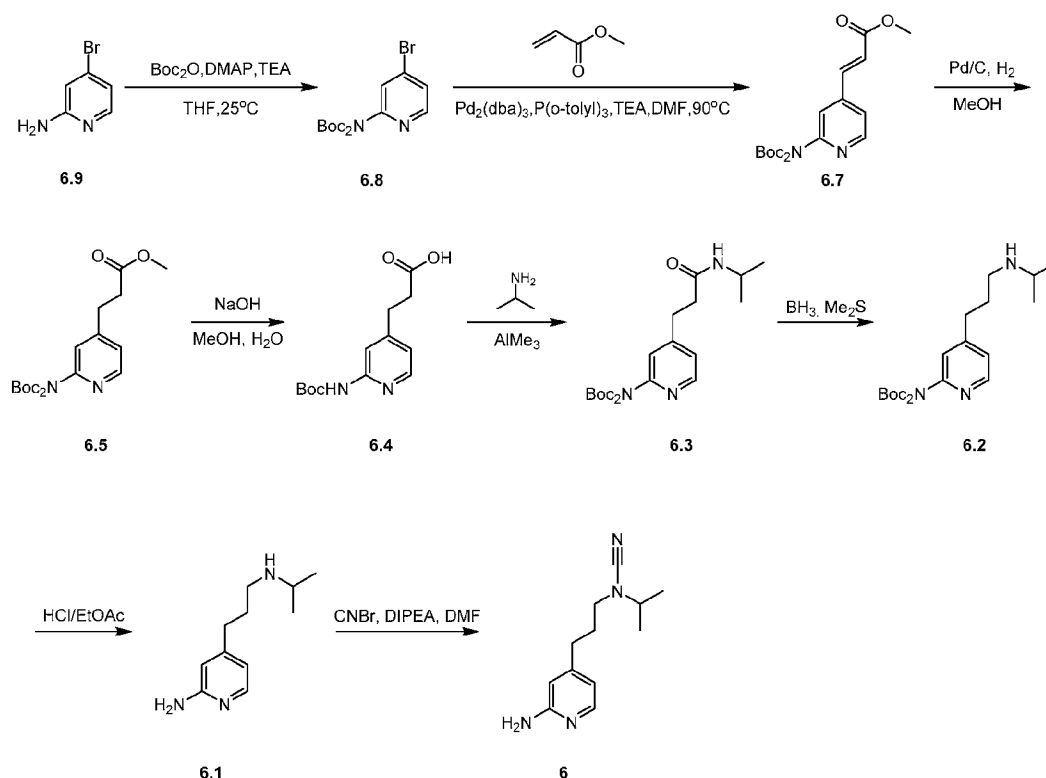
[0212] To a solution of compound **5.3** (800 mg, 3.37 mmol, 1 *eq*) in DCM (15 mL) was added acetone (195.80 mg, 3.37 mmol, 247.85 µL, 1 *eq*) in one portion at 25°C under N₂. Then the pH was adjusted to around 5 by progressively adding glacial acetic acid. The mixture was stirred at 25°C for 2 hour. Then the mixture was added NaBH(OAc)₃ (1.81 g, 8.56 mmol, 2.54 *eq*) in one portion at 0°C under N₂, then heated to 25 °C and stirred for 16 hours. The reaction was quenched by addition of 10 mL of H₂O, a clear yellow-brown solution was obtained which was extracted by DCM (3 x 15 mL). The residue was purified by prep-HPLC (TFA condition) to give compound **5.2** (400 mg, 1.43 mmol, 42.43% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₅H₂₅N₃O₂: 279; found 280; RT=1.473 min. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.33 (dd, *J*=6.50, 1.21 Hz, 13 H) 1.55 (s, 9 H) 2.97 - 3.12 (m, 5 H) 3.35 - 3.45 (m, 3 H) 6.83 (dd, *J*=6.73, 1.65 Hz, 1 H) 6.90 (dd, *J*=1.54, 0.66 Hz, 1 H) 7.20 (dd, *J*=5.73, 1.54 Hz, 1 H) 7.55 (d, *J*=0.66 Hz, 1 H) 7.78 (d, *J*=6.84 Hz, 1 H) 8.19 (d, *J*=5.95 Hz, 1 H).

[0213] Compound **5.2** (200 mg, 715.87 µmol, 1 *eq*) was added into a solution of HCl/EtOAc (5 mL). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was concentrated under reduced pressure to give compound **5.1** (180 mg, crude) as a yellow solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₀H₁₇N₃: 179; found 180; RT=0.250 min.

[0214] To a mixture of compound **5.1** (110 mg, 613.63 µmol, 1 *eq*) and DIEA (317.22 mg, 2.45 mmol, 428.68 µL, 4 *eq*) in THF (2 mL) was added dropwise a solution of BrCN (65 mg, 613.63 µmol, 45.14 µL, 1 *eq*) in THF (2 mL), and stirring at 0°C for 10 mins. The reaction mixture was partitioned between EtOAc 2 mL and water 2 mL. The organic phase was separated, washed with brine 2 mL (2 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by by prep-TLC (SiO₂, CH₃CN: EtOAc = 3:1) to give product **5** (11 mg, 53.85 µmol, 8.78% yield) as a light yellow oil. LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₆N₄: 204; found 205; RT=1.164 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.22 (d, *J*=6.62 Hz, 5 H) 2.80 - 2.89 (m, 1 H) 2.84 (t,

$J=7.28$ Hz, 1 H) 3.03 - 3.13 (m, 1 H) 3.20 (t, $J=7.28$ Hz, 2 H) 6.44 (s, 1 H) 6.53 (dd, $J=5.51$, 1.32 Hz, 1 H) 7.98 (d, $J=5.51$ Hz, 1 H).

Example 6. Preparation of *N*-(3-(2-aminopyridin-4-yl)propyl)-*N*-isopropylcyanamide (6)



- 5 [0215] To a solution of compound 6.9 (20 g, 115.60 mmol, 1 *eq*) in THF (400 mL) was added Boc_2O (63.07 g, 289 mmol, 66.39 mL, 2.50 *eq*), DMAP (4.24 g, 34.68 mmol, 0.30 *eq*) and TEA (35.09 g, 346.80 mmol, 48.07 mL, 3 *eq*) at 25°C under N_2 . The resulting mixture was stirred for 16 hours. The reaction mixture was added water 100 mL, extracted with EtOAc (300 mL x 3). The organic phase was separated, washed with NH_4Cl 100 mL and 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/Ethyl acetate = 5:1).
10 Compound 6.8 (27.70 g, 74.21 mmol, 64.20% yield) was obtained as a colorless oil.

- [0216] To a solution of compound 6.8 (27.70 g, 74.21 mmol, 1 *eq*) in DMF (460 mL) was added TEA (15.02 g, 148.43 mmol, 20.57 mL, 2 *eq*), $\text{P}(\text{o-tolyl})_3$ (6.78 g, 22.26 mmol, 0.30 *eq*), $\text{Pd}_2(\text{dba})_3$ (6.80 g, 7.42 mmol, 0.10 *eq*) and methyl prop-2-enoate (25.56 g, 296.86 mmol, 26.62 mL, 4 *eq*) in turn at 25°C under N_2 . The resulting mixture was stirred at 80°C for 13 hours. The reaction mixture was added H_2O 500 mL at 25°C, extracted with EtOAc (500 mL x 3). The combined organic layers were washed with saturated brine 200 mL (200 mL x 1),
15

dried over dry Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=50:1 to 10:1). Compound **6.7** (24 g, 63.42 mmol, 85.46% yield) was obtained as a white solid.

5 **[0217]** To a solution of compound **6.7** (24 g, 63.42 mmol, 1 *eq*) in MeOH (1.50 L) was added Pd-C under Ar_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25 °C for 24 hours. Pd/C was filtered off by filtration. The filtrate was concentrated to dry. Compound **6.6** (22 g, 57.83 mmol, 91.19% yield) was obtained as a white solid.

10 **[0218]** To a mixture of compound **6.5** (6 g, 15.77 mmol, 1 *eq*) in MeOH (60 mL) was added NaOH (1.89 g, 47.31 mmol, 3 *eq*) in one portion at 25°C. The mixture was stirred at 25°C for 17h. The pH was adjusted to around 4 by progressively adding citric acid. Then the solid was precipitate out, filtered to give compound **6.4** (4 g, 10.92 mmol, 69.22% yield) as a white solid. LCMS (ESI): m/z: [M - H] calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_4$: 265; found 265; RT=0.859
15 min. ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.45 - 1.59 (m, 7 H) 2.56 - 2.70 (m, 2 H) 2.83 - 2.98 (m, 2 H) 6.91 (dd, $J=5.18$, 1.43 Hz, 1 H) 7.71 (d, $J=0.66$ Hz, 1 H) 8.06 (d, $J=5.07$ Hz, 1 H).

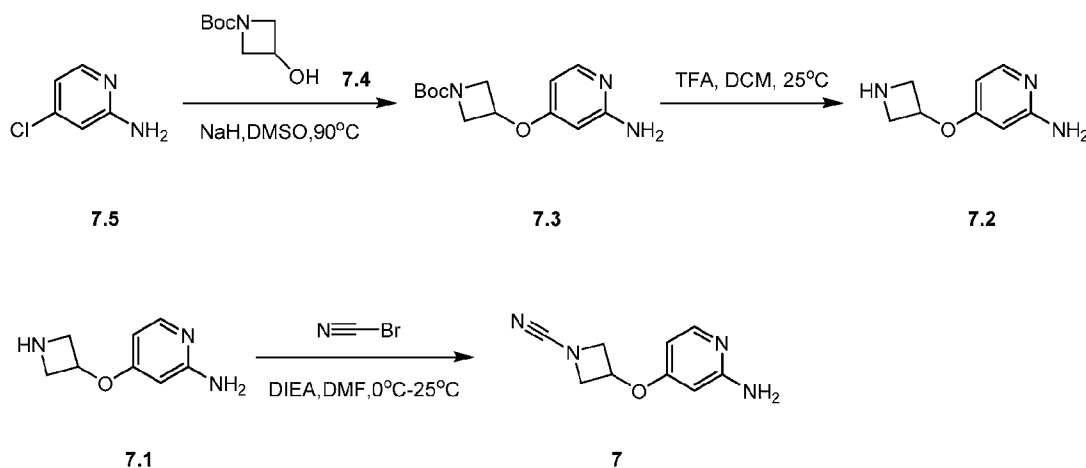
[0219] A solution of compound **6.4** (1 g, 2.63 mmol, 1 *eq*) was added in *i*-PrNH $_2$ (6.90 g, 116.73 mmol, 10 mL, 44.38 *eq*) at 25 °C. The mixture was added AlMe_3 (568.79 mg, 7.89
20 mmol, 3 mL, 3 *eq*) dropwised at 25 °C. The resulting mixture was stirred at 25 °C for 23 hours. The reaction mixture was filtered and concentrated under reduced pressure to give compound **6.3** (677 mg, 1.66 mmol, 63.17% yield).

[0220] To a solution of compound **6.3** (670 mg, 2.18 mmol, 1 *eq*) in THF (10 mL) was added a solution of $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 872 μL , 4 *eq*) dropwise with at 0°C over a period of 1
25 mins under N_2 . Then stirring at 25°C 4 hours. The reaction was quenched by addition of 6 ml methanol, then the reaction mixture was concentrated under reduced pressure to remove solvent. The mixture was further purification by pre-HPLC to give compound **6.2** (70 mg, 238.58 μmol , 10.94% yield) (70 mg, 238.58 μmol , 10.94% yield) as a white solid. LCMS (ESI): m/z: [M+H] calcd for $\text{C}_{16}\text{H}_{27}\text{N}_3\text{O}_2$: 294; found 294; RT=0.735 min.

[0221] To a mixture of compound **6.2** (70 mg, 177.88 μmol , 1 *eq*) in HCl/EtOAc (2 mL) at 25°C for 13 hours. The reaction mixture was concentrated under reduced pressure to give compound **6.1** (65 mg, crude) as light yellow oil.

[0222] To a mixture of compound **6.1** (63 mg, 236.66 μmol , 1 *eq*) and BrCN (25.07 mg, 236.66 μmol , 17.41 μL , 1 *eq*) in THF (3 mL) was added DIEA (122.34 mg, 946.64 μmol , 165.32 μL , 4 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 25 °C for 10 mins. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (3 mL x 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (neutral condition) to give **6** (10 mg, 45.81 μmol , 19.36% yield) as a yellow oil. LCMS (ESI): *m/z*: [M + H] calcd for C₁₂H₁₈N₄: 219; found 219; RT=2.279 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.25 - 1.28 (d, *J*=6.0 6 H) 1.90 - 2.10 (m, 2 H) 2.50 - 2.62 (m, 2 H) 2.96-2.99 (m, 2 H) 3.08-3.13 (m, 1 H) 4.37 (s, 2 H) 6.35(s, 1 H) 6.4 – 6.50(d, *J*=5.2 6 H) 7.98 – 7.99(d, *J*=5.2 1 H).

Example 7. Preparation of 3-((2-aminopyridin-4-yl)oxy)azetidine-1-carbonitrile (**7**)



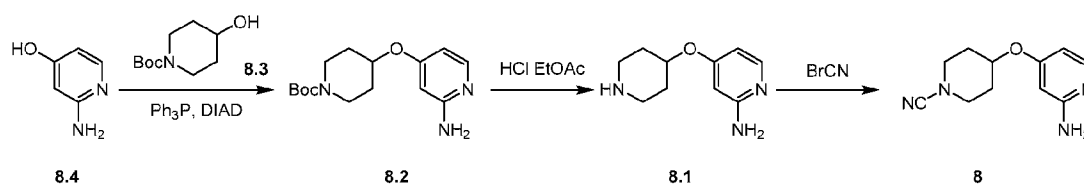
[0223] To a mixture of compound **7.4** (2 g, 11.55 mmol, 1 *eq*) in DMSO (40 mL) was added NaH (554.24 mg, 23.09 mmol, 2 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 2 hours, then added compound **7.5** (2.97 g, 23.09 mmol, 2 *eq*) to mixture and heated to 90 °C and stirred for 15 hours. The mixture was cooled to 25 °C and poured into ice-water (50 mL). The aqueous phase was extracted with ethyl acetate (40 mL x 3). The combined organic phase was washed with brine (30 mL x 1), dried with anhydrous Na₂SO₄ concentrated in vacuum to give a crude product as a brown solid. Then the crude product was purified by silica gel chromatography eluted with EtOAc : DCM=1 : 1 to give compound **7.2** (230 mg, 90%) as a brown oil. ¹H NMR (400 MHz, chloroform-*d*) ppm 1.46

(s, 9 H) 4 (dd, J=9.79, 3.76 Hz, 2 H) 4.33 (dd, J=9.54, 6.53 Hz, 2 H) 4.91 (t, J=3.76 Hz, 1 H) 5.91 - 6.01 (m, 1 H) 6.18 (dd, J=6.02, 1.51 Hz, 1 H) 7.84 (d, J=6.02 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₃H₁₉N₃O₃: 266; found 266; RT=1.547 min.

[0224] Compound **7.2** (230 mg, 866.91 μmol, 1 eq) was dissolved DCM (5 mL) and TFA (1 mL) at 25 °C under N₂. The mixture was stirred at 25 °C for 15 hours. The mixture was added small amount of water and acetonitrile, then work up it by lyophilization to give compound **7.1** (300 mg, 724.75 μmol, 83.60% yield, 95% purity, 2 TFA) as brown oil. The crude product was used for next step directly without purification. ¹H NMR (400 MHz, methanol-d₄) ppm 4.27 (dd, J=12.55, 4.52 Hz, 2 H) 4.63 (dd, J=12.80, 6.78 Hz, 2 H) 5.25 - 5.42 (m, 1 H) 6.27 (d, J=2.51 Hz, 1 H) 6.58 (dd, J=7.28, 2.26 Hz, 1 H) 7.81 (d, J=7.53 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₈H₁₁N₃O·2(C₂HF₃O₂):166; found 166; RT=0.214 min.

[0225] The mixture of compound **7.1** (50 mg, 302.68 μmol, 1 eq), TEA (30.63 mg, 302.68 μmol, 41.96 μL, 1 eq) and DIEA (117.36 mg, 908.04 μmol, 158.59 μL, 3 eq) in DCM (5 mL) was added dropwise solution of BrCN (32.06 mg, 302.68 μmol, 22.26 μL, 1 eq). The mixture was stirred at 25 °C for 10 min. The reaction mixture was quenched by addition H₂O 5mL at 25 °C, and then extracted with DCM (5 mL x 3). The combined organic layers were washed with saturated brines (3 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by prep-HPLC (TFA condition) to give the product **7** (13 mg, 68.35 μmol, 22.58% yield) as a white solid. ¹H NMR (400 MHz, chloroform-d) ppm 4.27 (dd, J=8.82, 4.41 Hz, 2 H) 4.44 (br. s., 2 H) 4.48 - 4.59 (m, 2 H) 4.98 (br. s., 1 H) 5.77 (s, 1 H) 6.02 - 6.15 (m, 1 H) 7.94 (d, J=5.73 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₉H₁₀N₄O:191; found 191; RT=1.014 min.

25 Example 8. Preparation of 4-((2-aminopyridin-4-yl)oxy)piperidine-1-carbonitrile (**8**)



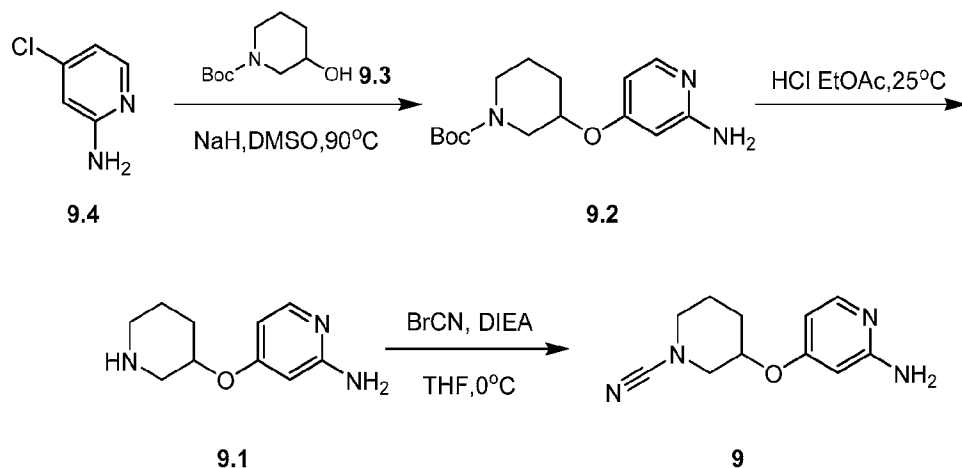
[0226] To a solution of compound **8.4** (500 mg, 4.54 mmol, 1 eq) in DCM (15 mL) was added compound **8.3** (913.90 mg, 4.54 mmol, 1 eq) PPh₃ (1.79 g, 6.81 mmol, 1.50 eq) and DIAD (1.38 g, 6.81 mmol, 1.32 mL, 1.50 eq) in turn at 0°C under N₂. The resulting mixture

was stirred at 25°C for 3 hours. The reaction mixture was added water 20 mL, extracted with EtOAc (20mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1).

- 5 Compound **8.2** (300 mg, 1.02 mmol, 22.52% yield) was obtained as a white solid. ¹H NMR (400 MHz, chloroform-d) ppm 1.47 (s, 9 H) 1.72 - 1.77 (m, 2 H) 1.88 - 1.93 (m, 2 H) 3.33 - 3.37 (m, 2 H) 3.64 - 3.68 (m, 2 H) 4.37 (s, 2 H) 4.47 - 4.51 (m, 1 H) 5.98 (d, J=2.0 Hz, 1 H) 6.25 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.90 (d, J= 6.0 Hz, 1 H).

- 10 **[0227]** A mixture of compound **8.2** (200 mg, 681.76 μmol, 1 *eq*) in EtOAc HCl (10 mL) was stirred at 25°C for 16 hours. The reaction mixture was filtered, the cake was washed with EtOAc (10 mL). The solid was removed solvent under reduced pressure. Compound **8.1** (100 mg, 435.33 μmol, 63.85% yield) was obtained as a white solid. ¹H NMR (400 MHz, D₂O-d₄) ppm 2.02 - 2.13 (m, 4 H) 3.18 - 3.36 (m, 4 H) 4.84 - 4.85 (m, 1 H) 6.33 (d, J=2.0 Hz, 1 H) 6.49 (dd, J=7.2 Hz, 2.0 Hz, 1 H) 7.69 (m, 1 H).

- 15 **[0228]** To a solution of compound **8.1** (50 mg, 217.67 μmol, 1 *eq*) in THF (5 mL) was added DIEA (28.13 mg, 217.67 μmol, 38.02 μL, 1 *eq*) and BrCN (23.06 mg, 217.67 μmol, 16.01 μL, 1 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 0°C for 2.5 hours. The reaction mixture was added water 5 mL, extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL x 1), dried over Na₂SO₄, filtered and
20 concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition). Product **8** (6.50 mg, 29.78 μmol, 13.68% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O:218; found 219; RT=1.934 min. ¹H NMR (400 MHz, chloroform-d) ppm 1.95 - 2.03 (m, 4 H) 3.23 - 3.48 (m, 4 H) 4.38 (s, 2 H) 4.56 (m, 1 H) 5.96 (s, 1 H) 6.24 (s, 1 H) 7.93 (d, J=5.2 Hz, 1 H).

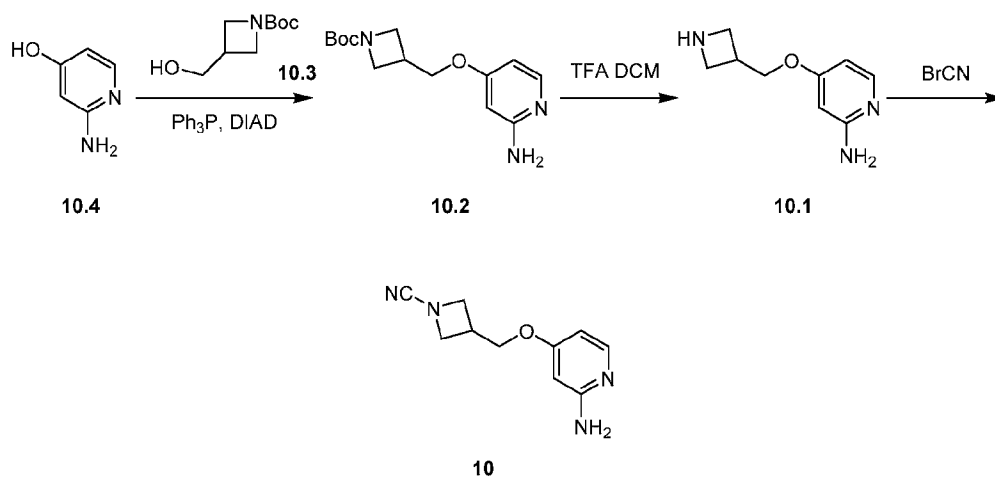
Example 9. Preparation of 3-((2-aminopyridin-4-yl)oxy)piperidine-1-carbonitrile (9)

[0229] To a mixture of compound **9.3** (2 g, 9.94 mmol, 1 *eq*) in DMSO (40 mL) was added NaH (476.99 mg, 19.88 mmol, 2 *eq*) in one portion. The mixture was stirred under N₂ at 25 °C for 2 hours, then added compound **9.4** (2.56 g, 19.88 mmol, 2 *eq*) to the mixture and heated to 90 °C and stirred for 15 hours. The mixture was cooled to 25 °C and poured into ice-water (50 mL). The aqueous phase was extracted with ethyl acetate (40 mL x 3). The combined organic phase was washed with brine (30 mL x 1), dried with anhydrous Na₂SO₄ concentrated in vacuum to give a crude product as a brown solid. Then the crude product was purified by silica gel chromatography eluted with (EtOAc : DCM=1 : 1) to give compound **9.2** (130 mg, 420.98 μmol, 4.24% yield, 95% purity) as a brown oil. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.17 - 1.49 (m, 9 H) 1.49 - 1.62 (m, 1 H) 1.74 - 2.06 (m, 3 H) 2.94 - 3.15 (m, 1 H) 3.32 - 4.14 (m, 3 H) 4.58 (br. s., 1 H) 6.32 (br. s., 1 H) 6.46 (d, *J*=5.29 Hz, 1 H) 7.59 - 7.81 (m, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₅H₂₃N₃O₃: 294; found 294; RT=1.046 min.

[0230] Compound **9.2** (130 mg, 443.14 μmol, 1 *eq*) was dissolved HCl/EtOAc (10 mL) and MeOH (5 mL) at 25 °C under N₂. The mixture was stirred at 25 °C for 5 h. The mixture was concentrated in vacuum to give compound **9.1** (80 mg, 393.27 μmol, 88.75% yield, 95% purity) as yellow oil. The crude product was used for next step directly without purification. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.79 - 1.91 (m, 1 H) 1.94 - 2.15 (m, 3 H) 3.17 (br. s., 1 H) 3.33 (br. s., 1 H) 3.39 - 3.63 (m, 3 H) 5.03 (br. s., 1 H) 6.49 (d, *J*=2.21 Hz, 1 H) 6.62 (dd, *J*=7.28, 2.43 Hz, 1 H) 7.77 (d, *J*=7.06 Hz, 1 H).

[0231] To a solution of compound **9.1** (80 mg, 413.97 μ mol, 1 *eq*) in THF (3 mL) and TEA (125.67 mg, 1.24 mmol, 172.15 μ L, 3 *eq*) was added a solution of BrCN (43.85 mg, 413.97 μ mol, 30.45 μ L, 1 *eq*) in THF (3 mL) drop-wise at 0°C under N₂. The reaction mixture was stirred at 0°C for 4 h. To the reaction mixture was added 4 mL water at 0°C. The aqueous phase was extracted with ethyl acetate (15 mL x 3). The combined organic phase was washed with brine (5 mL x 1), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by prep-TLC (neutral condition) to give product **9** (12 mg, 50.58 μ mol, 12.22% yield, 92% purity) as brown oil. ¹H NMR (400 MHz, methanol-d₄) ppm 1.59 - 1.72 (m, 1 H) 1.88 - 1.97 (m, 3 H) 3.34 - 3.41 (m, 1 H) 3.42 - 3.51 (m, 1 H) 4.62 - 4.72 (m, 1 H) 5.09 - 5.20 (m, 1 H) 6.22 - 6.32 (m, 1 H) 6.38 - 6.56 (m, 1 H) 7.65 - 7.80 (m, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O:219; found 219; RT=1.148 min.

Example 10. Preparation of 3-(((2-aminopyridin-4-yl)oxy)methyl)azetidine-1-carbonitrile (10)



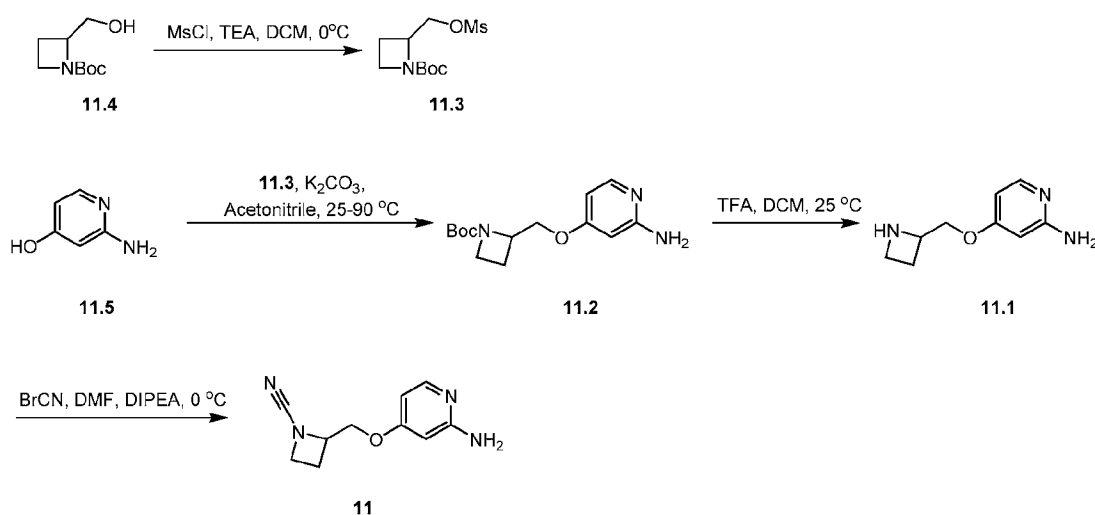
[0232] To a solution of compound **10.4** (1.50 g, 13.62 mmol, 1 *eq*) in DCM (15 mL) was added compound **10.3** (2.55 g, 13.62 mmol, 1 *eq*), PPh₃ (5.36 g, 20.43 mmol, 1.50 *eq*) and DIAD (4.13 g, 20.43 mmol, 3.97 mL, 1.50 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 25°C for 10 hours. The reaction mixture was added water 5 mL, extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (5 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1). Compound **10.2** (800 mg, 2.86 mmol, 21.03% yield) was obtained as a white solid. ¹H NMR (400 MHz, chloroform-d) ppm 1.46 (s, 9 H) 2.92 - 3 (m, 1 H) 3.75 - 3.79 (m, 2 H) 4.06 - 4.09

(m, 4 H) 4.39 (s, 2 H) 5.98 (d, J=2.0 Hz, 1 H) 6.26 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.90 (d, J= 5.6 Hz, 1 H)

[0233] To a solution of compound **10.2** (300 mg, 1.07 mmol, 1 *eq*) in DCM (5 mL) was added TFA (1.54 g, 13.50 mmol, 1 mL, 12.62 *eq*) at 25°C under N₂. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue and freezing dry. Compound **10.1** (500 mg, crude) was obtained as a white solid. ¹H NMR (400 MHz, D₂O-d₄) ppm 3.36 - 3.43 (m, 1 H) 4.40 - 4.12 (m, 2 H) 4.22 - 4.31 (m, 4 H) 6.42 (d, J=2.8 Hz, 1 H) 6.62 (dd, J=7.6 Hz, 2.4 Hz, 1 H) 7.69 (d, J=6.8 Hz, 1 H)

[0234] To a solution of compound **10.1** (300 mg, 736.61 μmol, 1 *eq*) in THF (5 mL) was added DIEA (285.60 mg, 2.21 mmol, 385.94 μL, 3 *eq*) and BrCN (78.02 mg, 736.61 μmol, 54.18 μL, 1 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 0°C for 1 hour. The reaction mixture was added water 10 mL, extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by p-TLC (SiO₂, Ethyl acetate = 0:1). Product **10** (14 mg, 68.55 μmol, 9.31% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₂N₄O:204; found 205; RT=1.750 min. ¹H NMR (400 MHz, chloroform-d) ppm 3.13 - 3.19 (m, 1 H) 4.08 - 4.11 (m, 4 H) 4.31 - 4.35 (m, 2 H) 4.96 (s, 2 H) 6.05 (d, J=2.0 Hz, 1 H) 6.30 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.88 (d, J=6.0 Hz, 1 H).

Example 11. Preparation of 2-(((2-aminopyridin-4-yl)oxy)methyl)azetidine-1-carbonitrile (**11**)



[0235] To a mixture of compound **11.4** (500 mg, 2.67 mmol, 1 eq) and TEA (540.35 mg, 5.34 mmol, 740.21 μ L, 2 eq) in DCM (10 mL) was added MsCl (367.02 mg, 3.20 mmol, 247.99 μ L, 1.20 eq) dropwise at 0°C under N₂. The reaction mixture was diluted with H₂O 10 mL and extracted with DCM 10 mL (10 mL x 3). The combined organic layers were washed
5 with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **11.3** (850 mg, crude) as a yellow oil. (Combined with a second batch to afford a total of 1.3 g). LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₉NSO₅: 265; found 166,210; RT=0.657, 0.693 min.

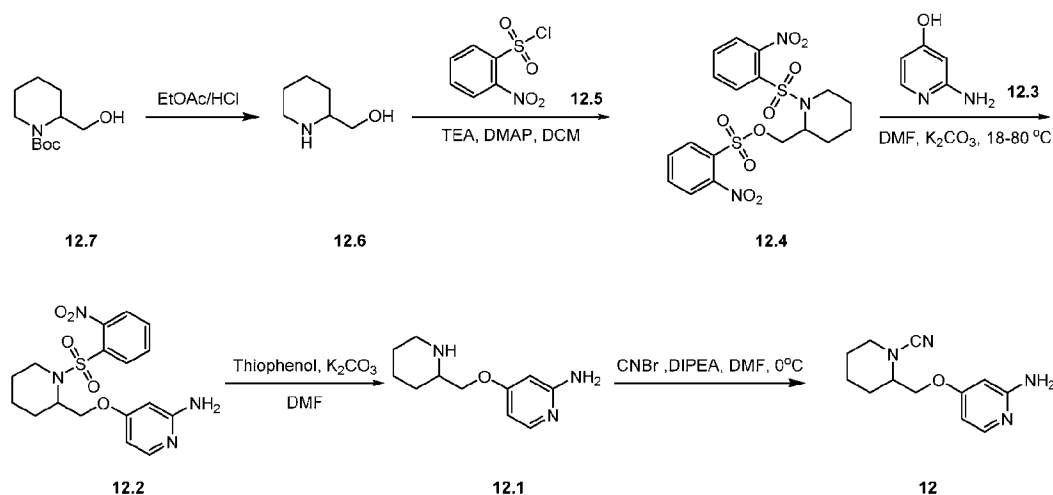
[0236] To a mixture of compound **11.3** (1 g, 3.77 mmol, 1 eq) and compound **11.5** (414.99
10 mg, 3.77 mmol, 1 eq) in acetonitrile (15 mL) was added K₂CO₃ (1.04 g, 7.54 mmol, 2 eq) in one portion at 25°C under N₂. Then heated to 90 °C and stirred for 10 hours. The reaction mixture was diluted with H₂O 15 mL and extracted with EA 10 mL (10 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Then the residue was
15 purified by column (SiO₂, DCM/MeOH=10:1) to give compound **11.2** (200 mg, 716 μ mol, 18.99% yield) as a white solid. ¹H NMR (400 MHz, chloroform-d) ppm 1.42 (s, 9 H) 1.45 (s, 18 H) 1.78 (br. s., 3 H) 2.17 - 2.41 (m, 6 H) 2.98 - 3.12 (m, 6 H) 3.73 - 3.93 (m, 6 H) 4.21 - 4.33 (m, 3 H) 4.35 - 4.63 (m, 6 H) 6.03 (d, J=1.51 Hz, 1 H) 6.30 (dd, J=6.02, 2.01 Hz, 1 H) 7.89 (d, J=6.02 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₄H₂₁N₃O₃: 279; found 187;
20 RT=0.576, 0.630 min.

[0237] To a solution of compound **11.2** (200 mg, 716 μ mol, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 18.86 eq) in one portion at 25°C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **11.1** (240 mg, crude) as a light yellow solid. LCMS
25 (ESI): m/z: [M + H] calcd for C₉H₁₃N₃O: 179; found 180; RT=0.175, 0.240 min.

[0238] To a mixture of compound **11.1** (50 mg, 278.99 μ mol, 1 eq) and DIPEA (144.23 mg, 1.12 mmol, 194.91 μ L, 4 eq) in DCM (2 mL) was added a solution of carbononitridic bromide (29.55 mg, 278.99 μ mol, 20.52 μ L, 1 eq) in 0.5 mL DCM dropwise at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins. The reaction mixture was diluted with H₂O 2 mL
30 and extracted with DCM 2 mL (2 mL x 3). The combined organic layers were washed with brine 3 mL (3 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Then, the residue was purified by prep-HPLC (TFA condition) to give

product **11** (10 mg, 48.96 μ mol, 17.55% yield) as a yellow solid. ^1H NMR (400 MHz, chloroform- d) ppm 2.32 - 2.43 (m, 1 H) 2.43 - 2.54 (m, 1 H) 4.06 - 4.25 (m, 3 H) 4.43 (br. s., 1 H) 4.64 - 4.77 (m, 1 H) 6.03 (d, $J=2.01$ Hz, 1 H) 6.30 (dd, $J=5.52, 2.01$ Hz, 1 H) 7.94 (d, $J=6.02$ Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$: 204; found 205; RT=1.754 min.

Example 12. Preparation of 2-(((2-aminopyridin-4-yl)oxy)methyl)piperidine-1-carbonitrile (12)



[0239] Compound **12.7** (2 g, 9.29 mmol, 1 *eq*) was added into HCl/EtOAc (20 mL), the reaction was stirred for 15 hours at 18 $^\circ\text{C}$. The reaction mixture was concentrated under reduced pressure to give compound **12.6** (2.10 g, crude) as a white solid.

[0240] To a mixture of compound **12.6** (2.10 g, 11.16 mmol, 1 *eq*, 2HCl) and TEA (3.39 g, 33.48 mmol, 4.64 mL, 3 *eq*) in DCM (25 mL) was added compound **12.5** (5.19 g, 23.44 mmol, 2.10 *eq*) in one portion at 0 $^\circ\text{C}$. The mixture was then heated to 18 $^\circ\text{C}$ and stirred for 15 hours. The reaction mixture was quenched by addition H_2O 20 mL and then diluted with DCM 10 mL and extracted with DCM 20 mL (20 mL \times 3). The combined organic layers were washed with brine 40 mL (40 mL \times 1), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give compound **12.4** (4.50 g, crude) as a yellow solid. LCMS (ESI): m/z : $[\text{M} - \text{H}]$ calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_9\text{S}_2$: 485; found 486; RT=0.869 min.

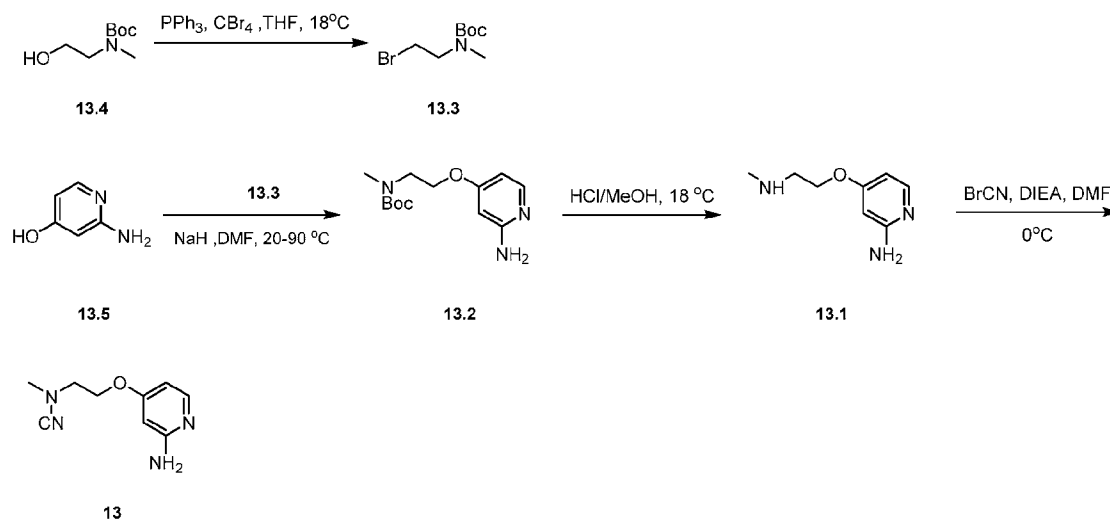
[0241] To a mixture of compound **12.4** (4.50 g, 9.27 mmol, 1 *eq*) and compound **12.3** (1.22 g, 11.12 mmol, 1.20 *eq*) in DMF (50 mL) was added K_2CO_3 (2.56 g, 18.54 mmol, 2 *eq*) in one portion at 18 $^\circ\text{C}$ under N_2 . Then heated to 80 $^\circ\text{C}$ and stirred for 15 hours. The reaction mixture was diluted with H_2O 50 mL and extracted with EtOAc 120 mL (40 mL \times 3). The

combined organic layers were washed with brine 80 mL (80 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1) to give compound **12.2** (260 mg, 662.54 μmol, 7.15% yield) as a yellow solid. LCMS (ESI): m/z: [M - H] calcd for C₁₇H₂₀N₄O₅S: 392; found 393; RT=0.714 min.

[0242] To a mixture of compound **12.2** (260 mg, 662.54 μmol, 1 eq) and K₂CO₃ (366.28 mg, 2.65 mmol, 4 eq) in DMF (2 mL) was added THIOPHENOL (146 mg, 1.33 mmol, 135.18 μL, 2 eq) dropwise at 18°C under N₂. The mixture was stirred at 18 °C for 4 hours. The residue was purified by prep-HPLC (TFA condition) to give compound **12.1** (80 mg, 385.97 μmol, 58.26% yield) as a white solid. LCMS (ESI): m/z: [M - H] calcd for C₁₁H₁₇N₃O: 207; found 208; RT=1.039 min. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.60 - 1.83 (m, 2 H) 1.91 - 2.10 (m, 2 H) 3.04 - 3.18 (m, 1 H) 3.49 (br d, *J*=12.80 Hz, 1 H) 3.65 (td, *J*=7.37, 3.45 Hz, 1 H) 4.27 (dd, *J*=10.79, 7.28 Hz, 1 H) 4.41 (dd, *J*=10.79, 3.39 Hz, 1 H) 6.45 (d, *J*=2.51 Hz, 1 H) 6.62 (dd, *J*=7.28, 2.51 Hz, 1 H) 7.79 (d, *J*=7.28 Hz, 1 H)

[0243] To a mixture of compound **12.1** (70 mg, 337.72 μmol, 1 eq) and DIEA (174.59 mg, 1.35 mmol, 235.93 μL, 4 eq) in DMF (3 mL) was added carbononitridic bromide (35.77 mg, 337.72 μmol, 24.84 μL, 1 eq) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins. The reaction mixture diluted with H₂O 3 mL and extracted with DCM 9 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **12** (15 mg, 64.58 μmol, 19.12% yield) as a yellow solid. LCMS (ESI): m/z: [M - H] calcd for C₁₂H₁₆N₄O: 232; found 233; RT= 1.970 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.48 (br d, *J*=8.03 Hz, 2 H) 1.60 (br s, 1 H) 1.74 (br d, *J*=6.65 Hz, 2 H) 3.10 - 3.19 (m, 1 H) 3.43 (br s, 1 H) 3.54 (br s, 1 H) 4.29 (d, *J*=4.89 Hz, 2 H) 6.38 (d, *J*=2.38 Hz, 1 H) 6.57 (dd, *J*=7.28, 2.51 Hz, 1 H) 7.83 (br s, 2 H) 7.87 (d, *J*=7.28 Hz, 1 H)

Example 13. Preparation of *N*-(2-((2-aminopyridin-4-yl)oxy)ethyl)-*N*-methylcyanamide (13)



[0244] To a mixture of compound **13.4** (2 g, 11.41 mmol, 1 *eq*) and CBr₄ (5.68 g, 17.11 mmol, 1.50 *eq*) in THF (20 mL) was added PPh₃ (4.49 g, 17.11 mmol, 1.50 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 1 hour. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM) to give compound **13.3** (1.80 g, 7.56 mmol, 66.25% yield) as a colorless oil. ¹H NMR (400 MHz, chloroform-d) ppm 1.31 - 1.47 (m, 9 H) 2.80 - 2.91 (m, 3 H) 3.37 (br. s., 2 H) 3.46 - 3.59 (m, 2 H).

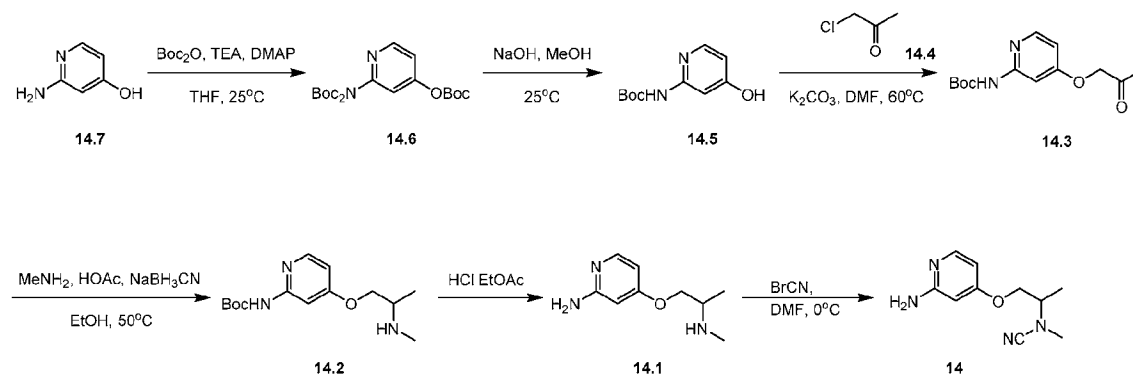
[0245] To a solution of compound **13.5** (832.35 mg, 7.56 mmol, 1 *eq*) in DMF (2 mL) was added NaH (362.84 mg, 15.12 mmol, 2 *eq*) portionwise at 20 °C under N₂. The mixture was stirred at 20 °C for 0.5 hour. Then the mixture was added compound **13.3** (1.80 g, 7.56 mmol, 1 *eq*) in one portion and heated to 90 °C stirred for 14.5 hours. The reaction mixture was diluted with H₂O 3 mL and extracted with EA 2 mL (2 mL x 3). The combined organic layers were washed with brine 5 mL (5 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **13.2** (1 g, crude) as a yellow oil. ¹H NMR (400 MHz, methanol-d₄) δ ppm 1.37 - 1.56 (m, 9 H) 2.86 (s, 4 H) 2.94 (br. s., 2 H) 2.99 (s, 5 H) 3.54 - 3.68 (m, 1 H) 4.01 - 4.16 (m, 2 H) 6.10 (d, J=2.21 Hz, 1 H) 6.18 - 6.32 (m, 1 H) 7.70 (d, J=5.73 Hz, 1 H) 7.98 (s, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₃H₂₁N₃O₃: 267; found 268; RT=0.631, 0.833 min.

[0246] Compound **13.2** (500 mg, 1.87 mmol, 1 *eq*) was added into a solution of HCl/MeOH (8 mL). The mixture was stirred at 18 °C for 15 hours. The reaction mixture was

concentrated under reduced pressure to give compound **13.1** (300 mg, 1.79 mmol, 95.94% yield) as a yellow solid. LCMS (ESI): m/z : $[M + H]^+$ calcd for $C_8H_{13}N_3O$: 167; found 168; RT=0.166, 0.258 min.

[0247] To a mixture of compound **13.1** (150 mg, 897.08 μ mol, 1 *eq*) and DIEA (463.75 mg, 3.59 mmol, 626.69 μ L, 4 *eq*) in DCM (3 mL) was added carbononitridic bromide (95.02 mg, 897.08 μ mol, 65.98 μ L, 1 *eq*) in one portion at 0°C under N_2 . The mixture was stirred at 0°C for 30 mins. The reaction mixture diluted with H_2O 3 mL and extracted with DCM 3 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **13** (10 mg, 52.02 μ mol, 5.80% yield) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ ppm 2.83 - 2.93 (m, 3 H) 3.37 (t, $J=4.85$ Hz, 2 H) 4.06 - 4.15 (m, 2 H) 5.90 (br. s., 2 H) 5.99 (d, $J=2.21$ Hz, 1 H) 6.11 - 6.21 (m, 1 H) 7.74 (d, $J=6.17$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]^+$ calcd for $C_9H_{14}N_4O$: 192; found 193; RT=0.508 min.

Example 14. Preparation of N-(1-((2-aminopyridin-4-yl)oxy)propan-2-yl)-N-methylcyanamide (14)



[0248] To a solution of compound **14.7** (1 g, 9.08 mmol, 1 *eq*) in THF (20 mL) was added Boc_2O (5.95 g, 27.24 mmol, 6.26 mL, 3 *eq*), TEA (3.68 g, 36.32 mmol, 5.03 mL, 4 *eq*) and DMAP (332.79 mg, 2.72 mmol, 0.30 *eq*) at 25°C under N_2 . The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water (30 mL), extracted with EtOAc (50 mL x 3). The organic phase was separated, washed with saturated $NaCl$ (30 mL) and 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/Ethyl acetate=20:1 to 3:1). Compound **14.6** (1.50 g, 3.65 mmol, 40.25% yield) was obtained as a yellow solid.

[0249] To a solution of compound **14.6** (1.50 g, 3.65 mmol, 1 eq) in MeOH (20 mL) was added NaOH (438 mg, 10.95 mmol, 3 eq) at 25°C under N₂. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water (30 mL), extracted with EtOAc (50 mL x 3). The organic phase was separated, washed with saturated NaCl (30 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20:1 to 3:1). Compound **14.5** (550 mg, 2.62 mmol, 71.68% yield) was obtained as a white solid.

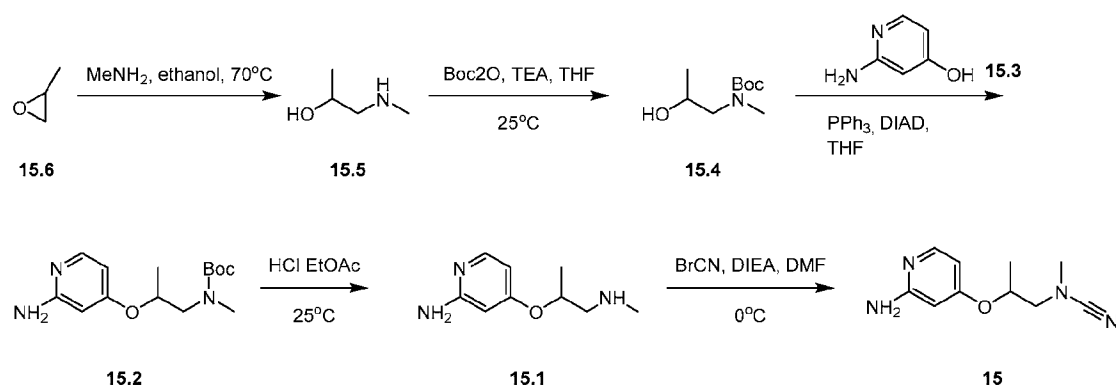
[0250] To a mixture of compound **14.5** (500 mg, 2.38 mmol, 1 eq) and compound **14.4** (330.30 mg, 3.57 mmol, 1.50 eq) in DMSO (20 mL) was added K₂CO₃ (657.88 mg, 4.76 mmol, 2 eq) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 15 hours. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. Compound **14.3** (900 mg, crude) was obtained as a colorless oil. ¹H NMR (400 MHz, chloroform-d) ppm 1.54 (s, 9 H), 2.29 (s, 3 H), 4.63 (s, 2 H), 6.52 (dd, *J*=5.6 Hz, 2.0 Hz, 1 H), 7.58 (d, *J*=2.0 Hz, 1 H), 8.13 (d, *J*= 6.0 Hz, 1 H), 9.12 (s, 1 H).

[0251] To a mixture of compound **14.3** (360 mg, 1.35 mmol, 1 eq) and methanamine (2 M, 1.35 mL, 2 eq) in EtOH (2 mL) was added CH₃COOH (40.59 mg, 675.95 μmol, 38.66 μL, 0.50 eq) and NaBH₃CN (212.38 mg, 3.38 mmol, 2.50 eq) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 20 hours. The mixture was diluted with water (5 mL), neutralized with solid NaHCO₃ until no CO₂ was evolved. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 0:1). Compound **14.2** (110 mg, 390.97 μmol, 28.96% yield) was obtained as a colorless oil. ¹H NMR (400 MHz, chloroform-d) ppm 1.18 (d, *J*= 6.4 Hz, 3 H), 1.53 (s, 9 H), 2.49 (s, 3 H), 3.03 - 3.06 (m, 1 H), 3.89 - 4.02 (m, 2 H), 6.53 (dd, *J*=5.6 Hz, 2.4 Hz, 1 H), 7.54 (d, *J*=2.4 Hz, 1 H), 8.04 (d, *J*= 6.0 Hz, 1 H).

[0252] To a solution of compound **14.2** (110 mg, 390.97 μmol, 1 eq) in HCl/EtOAc (20 mL) at 20°C under N₂. The mixture was stirred at 20 °C for 15 hours. Filtered and concentrated in vacuum. Filtered and concentrated in vacuum. Compound **14.1** (110 mg, 378.50 μmol, 96.81% yield, 3HCl) was obtained as a black brown solid. ¹H NMR (400 MHz, methanol-d₄) ppm 1.46 (d, *J*= 6.8 Hz, 3 H), 2.78 (s, 3 H), 2.73 - 2.75 (m, 1 H), 2.49 (s, 3 H), 4.29 - 4.49 (m, 2 H), 6.46 (d, *J*=2.4 Hz, 1 H), 6.63 (dd, *J*=2.4 Hz, *J*=7.2 Hz, 1 H), 7.78 (d, *J*= 7.2 Hz, 1 H).

[0253] To a mixture of compound **14.1** (80 mg, 441.43 μ mol, 1 eq) and carbononitridic bromide (46.76 mg, 441.43 μ mol, 32.47 μ L, 1 eq) in DMF (1 mL) was added DIEA (228.20 mg, 1.77 mmol, 308.38 μ L, 4 eq) in one portion at 0°C under N₂. The mixture was stirred at 0°C for 10 mins. The residue was purified by prep-HPLC (basic condition). Product **14** (10 mg, 48.49 μ mol, 10.98% yield) was obtained as a black brown solid. ¹H NMR (400 MHz, DMSO-d₆) ppm 1.22 (d, *J*= 6.8 Hz, 3 H), 2.87 (s, 3 H), 3.43 - 3.45 (m, 1 H), 3.89 - 4.02 (m, 2 H), 5.83 (s, 2 H), 5.97 (d, *J*=2.4 Hz, 1 H), 6.16 (dd, *J*=2.0 Hz, *J*=5.6 Hz, 1 H), 7.73 (d, *J*=6.0 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₀H₁₄N₄O: 207; found 207; RT=1.842 min.

10 **Example 15. Preparation of *N*-(2-((2-aminopyridin-4-yl)oxy)propyl)-*N*-methylcyanamide (15)**



[0254] The solution of compound **15.6** (1 g, 17.22 mmol, 1.20 mL, 1 eq) in MeNH₂ (ethanol solution) (534.80 mg, 17.22 mmol, 3 mL, 1 eq) was stirred at 70 °C for 15 hour. The mixture was concentrated under reduced pressure to give a residue. The crude product compound **15.5** (1 g, 11.22 mmol, 65.15 % yield) was used into the next step without further purification. ¹H NMR (400 MHz, chloroform-*d*) ppm 1.05 - 1.16 (m, 3 H) 2.27 - 2.46 (m, 4 H) 2.57 (dd, *J*=12.13, 2.87 Hz, 1 H) 3.79 (d, *J*=6.17 Hz, 1 H).

[0255] To a solution of compound **15.5** (1 g, 11.22 mmol, 1 eq) in THF (10 mL) was added TEA (2.27 g, 22.44 mmol, 3.11 mL, 2 eq) and Boc₂O (3.67 g, 16.83 mmol, 3.87 mL, 1.50 eq). The mixture was stirred at 25°C for 15 hours. The reaction mixture was quenched by addition H₂O 15 mL at 25°C, and extracted with DCM (20 mL x 3). The combined organic layers were washed with saturated brines (15 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum : ether/Ethyl acetate=2:1) to give compound **15.4** (1.30 g, 6.87 mmol, 61.22% yield) as a yellow oil. ¹H NMR (400 MHz,

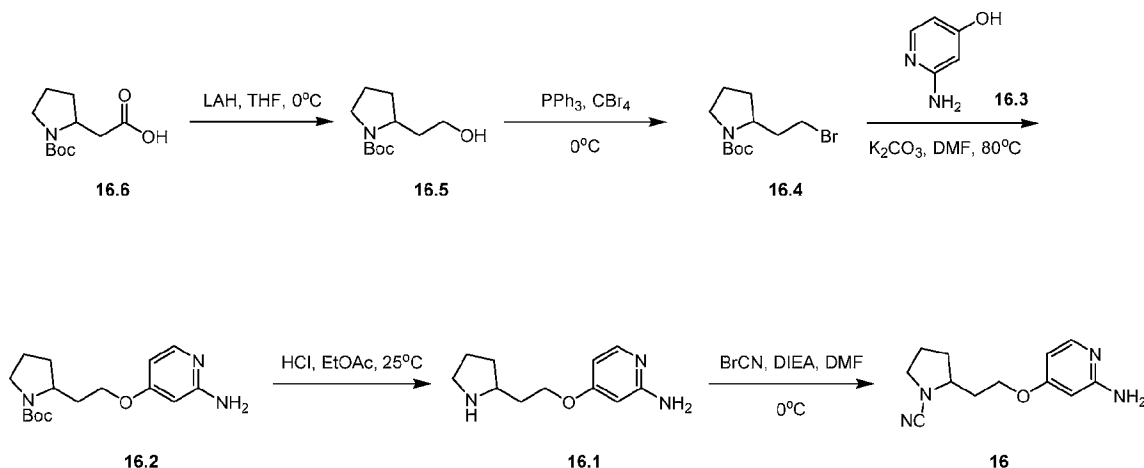
chloroform-*d*) ppm 1.15 (d, *J*=6.17 Hz, 3 H) 1.36 - 1.54 (m, 9 H) 2.91 (s, 3 H) 3.03 - 3.43 (m, 2 H) 3.88 - 4.13 (m, 1 H).

[0256] To a solution of compound **15.4** (1.20 g, 6.34 mmol, 1 *eq*) and compound **15.3** (698.19 mg, 6.34 mmol, 1 *eq*) in DCM (20 mL) was added PPh₃ (2.49 g, 9.51 mmol, 1.50 *eq*) and DIAD (1.92 g, 9.51 mmol, 1.85 mL, 1.50 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O 25 mL at 25 °C, and extracted with DCM (20 mL x 3). The combined organic layers were washed with saturated brines (15 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The crude product was purified by column chromatography (SiO₂, Petroleum : ether/Ethyl acetate=1:1) to give compound **15.2** (200 mg, crude) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.21 - 1.31 (m, 4 H) 1.34 (d, *J*=6.02 Hz, 6 H) 1.46 (br. s., 10 H) 2.05 (s, 1 H) 2.75 - 3.05 (m, 3 H) 4.13 (d, *J*=7.53 Hz, 1 H) 4.35 (br. s., 3 H) 4.50 - 4.77 (m, 2 H) 5.90 - 6.11 (m, 2 H) 6.24 (dd, *J*=6.02, 2.01 Hz, 2 H) 7.89 (d, *J*=6.02 Hz, 2 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₄H₂₃N₃O₃: 282; found 282; RT=0.705 min.

[0257] A mixture of compound **15.2** (200 mg, 710.86 μmol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 1 hour. The reaction mixture concentrated under reduced pressure to give a crude product compound **15.1** (120 mg, crude, 2 HCl) as a white solid. ¹H NMR (400 MHz, methanol-*d*₄) ppm 1.24 (s, 2 H) 1.39 (d, *J*=6.02 Hz, 4 H) 1.45 (d, *J*=6.02 Hz, 3 H) 2.78 (s, 3 H) 3.35 - 3.45 (m, 2 H) 4.72 - 4.83 (m, 1 H) 4.99 - 5.11 (m, 1 H) 6.36 (s, 1 H) 6.49 (s, 1 H) 6.52 (d, *J*=2.51 Hz, 1 H) 6.63 (s, 1 H) 7.65 - 7.73 (m, 1 H) 7.78 (d, *J*=7.53 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₉H₁₅N₃O: 182; found 182; RT=0.092 min.

[0258] To a solution of compound **15.1** (120 mg, 472.14 μmol, 1 *eq*, 2HCl) in DMF (1.50 mL) was added DIEA (244.08 mg, 1.89 mmol, 329.84 μL, 4 *eq*) and BrCN (50.01 mg, 472.14 μmol, 34.73 μL, 1 *eq*). The mixture was stirred at 0 °C for 10 mins. The residue was purified by prep-HPLC (neutral condition) to give the product product **15** (3 mg, 14.55 μmol, 3.08% yield) as a white solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.35 (d, *J*=6.02 Hz, 3 H) 2.96 (s, 3 H) 3.23 - 3.32 (m, 2 H) 4.72 - 4.82 (m, 1 H) 6.16 (d, *J*=2.01 Hz, 1 H) 6.30 (dd, *J*=6.02, 2.51 Hz, 1 H) 7.69 - 7.81 (m, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₄H₂₃N₃O₃: 207; found 207; RT=1.083 min.

Example 16. Preparation of 2-(2-((2-aminopyridin-4-yl)oxy)ethyl)pyrrolidine-1-carbonitrile (16)



[0259] To a mixture of compound **16.6** (2 g, 8.72 mmol, 1 *eq*) in THF (20 mL) was added LAH (661.85 mg, 17.44 mmol, 2 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 2 hours. After the reaction mixture was cooled to 0 °C, the reaction mixture was quenched by addition of 5 mL of H₂O, followed by 2 mL of 15% aqueous NaOH. After being stirred at room temperature for 10 mins, the solid was removed by filtration. The filtrate was concentrated to dryness to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 2:1). Compound **16.5** (1.38 g, 6.41 mmol, 73.51% yield) was obtained as a colorless oil.

[0260] To a mixture of compound **16.5** (800 mg, 3.72 mmol, 1 *eq*) and carbon tetrabromide (1.85 g, 5.58 mmol, 1.50 *eq*) in THF (15 mL) was added PPh₃ (1.46 g, 5.58 mmol, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 2 hours. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate=20/1 to 5:1). Compound **16.4** (640 mg, 2.30 mmol, 61.84% yield) was obtained as a colorless oil. LCMS (ESI): m/z: [M + H - 56] called for C₁₂H₂₀BrNO₂: 222; found 222; RT=0.103 min.

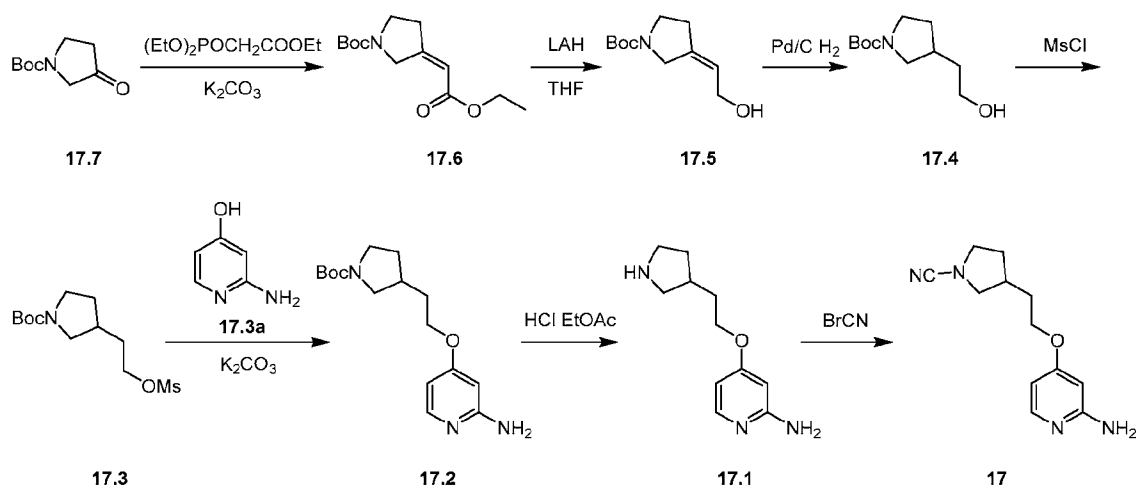
[0261] To a mixture of compound **16.4** (300 mg, 1.08 mmol, 1 *eq*) and compound **16.3** (118.92 mg, 1.08 mmol, 1 *eq*) in DMF (10 mL) was added K₂CO₃ (298.53 mg, 2.16 mmol, 2 *eq*) in one portion at 15°C under N₂. The mixture was stirred at 80 °C for 2 hours. The aqueous phase was extracted with ethyl acetate (10 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in

vacuum. Compound **16.2** (70 mg, crude) was obtained as black brown oil. It was combined with a second batch for a total of 140 mg, crude. LCMS (ESI): m/z : $[M + H]^+$ called for $C_{16}H_{25}N_3O_3$: 308; found 308; $RT=0.689$ min.

[0262] A mixture of compound **16.2** (140 mg, 455.45 μ mol, 1 *eq*) in HCl/EtOAc (10 mL) was stirred at 15 °C for 15 hours. The mixture was concentrated in vacuum to give crude product. Compound **16.1** (75 mg, 361.85 μ mol, 79.45% yield) was obtained as a colorless oil. LCMS (ESI): m/z : $[M + H]^+$ called for $C_{11}H_{17}N_3O$: 208; found 208; $RT=0.102$ min.

[0263] To a mixture of compound **16.1** (75 mg, 361.85 μ mol, 1 *eq*) and DIEA (93.53 mg, 723.69 μ mol, 126.39 μ L, 2 *eq*) in DMF (2 mL) was added carbononitridic bromide (38.33 mg, 361.85 μ mol, 26.62 μ L, 1 *eq*) in one portion at 0 °C under N_2 . The mixture was stirred at 15 °C for 15 hours. The residue was purified by prep-HPLC (basic conditions). Product **16** (2 mg, 8.61 μ mol, 2.38% yield) was obtained as a white solid. 1H NMR (400 MHz, methanol- d_4) δ ppm 1.57 - 1.79 (m, 1 H) 1.84 - 2.29 (m, 5 H) 2.92 (br d, $J=13.23$ Hz, 1 H) 3.38 - 3.58 (m, 2 H) 3.83 (quin, $J=6.73$ Hz, 1 H) 4.02 - 4.26 (m, 2 H) 6.10 (d, $J=2.21$ Hz, 1 H) 6.25 (dd, $J=6.06, 2.32$ Hz, 1 H) 7.70 (d, $J=6.17$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]^+$ called for $C_{12}H_{16}N_4O$: 233; found 233; $RT=0.983$ min.

Example 17. Preparation of 3-(2-((2-aminopyridin-4-yl)oxy)ethyl)pyrrolidine-1-carbonitrile (**17**)



[0264] To a mixture of ethyl 2-diethoxyphosphorylacetate (20 g, 89.21 mmol, 17.70 mL, 1 *eq*) and K_2CO_3 (30.82 g, 223.03 mmol, 2.50 *eq*) in DMF (100 mL) was added compound **17.7** (19.83 g, 107.05 mmol, 1.20 *eq*) in one portion at 20 °C under N_2 . The mixture was stirred at 50 °C for 15 hours. The aqueous phase was extracted with EtOAc (50 mL x 3). The combined

organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1). Compound **17.6** (7 g, 27.42 mmol, 30.73% yield) was obtained as a colorless oil.

- 5 **[0265]** To a mixture of compound **17.6** (3 g, 11.75 mmol, 1 *eq*) in THF (60 mL) was added LAH (2.23 g, 58.75 mmol, 5 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0°C for 2 hours. After the reaction mixture was cooled to 0°C, the reaction mixture was quenched by addition of 50 mL of H₂O, followed by 10 mL of 15% aqueous NaOH. After being stirred at room temperature for 10 mins, the solid was removed by filtration. The
10 filtrate was concentrated to dryness to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 4:1). Compound **17.5** (1.07 g, 5.02 mmol, 42.70% yield) was obtained as a colorless oil.

- 15 **[0266]** To a solution of compound **17.5** (670 mg, 3.14 mmol, 1 *eq*) in MeOH (10 mL) was added Pd/C (200 mg, 10% purity) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (15psi) at 15°C for 3 hours. The reaction mixture was filtered and the filter was concentrated. Compound **17.4** (500 mg, 2.32 mmol, 73.96% yield) was obtained as a colorless oil.

- 20 **[0267]** To a mixture of compound **17.4** (400 mg, 1.86 mmol, 1 *eq*) and methanesulfonyl chloride (319.24 mg, 2.79 mmol, 215.71 µL, 1.50 *eq*) in DCM (2 mL) was added TEA (376.01 mg, 3.72 mmol, 515.09 µL, 2 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 2 hours. The aqueous phase was extracted with EtOAc (20mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. Compound **17.3** (400 mg, crude) was obtained as a colorless oil.

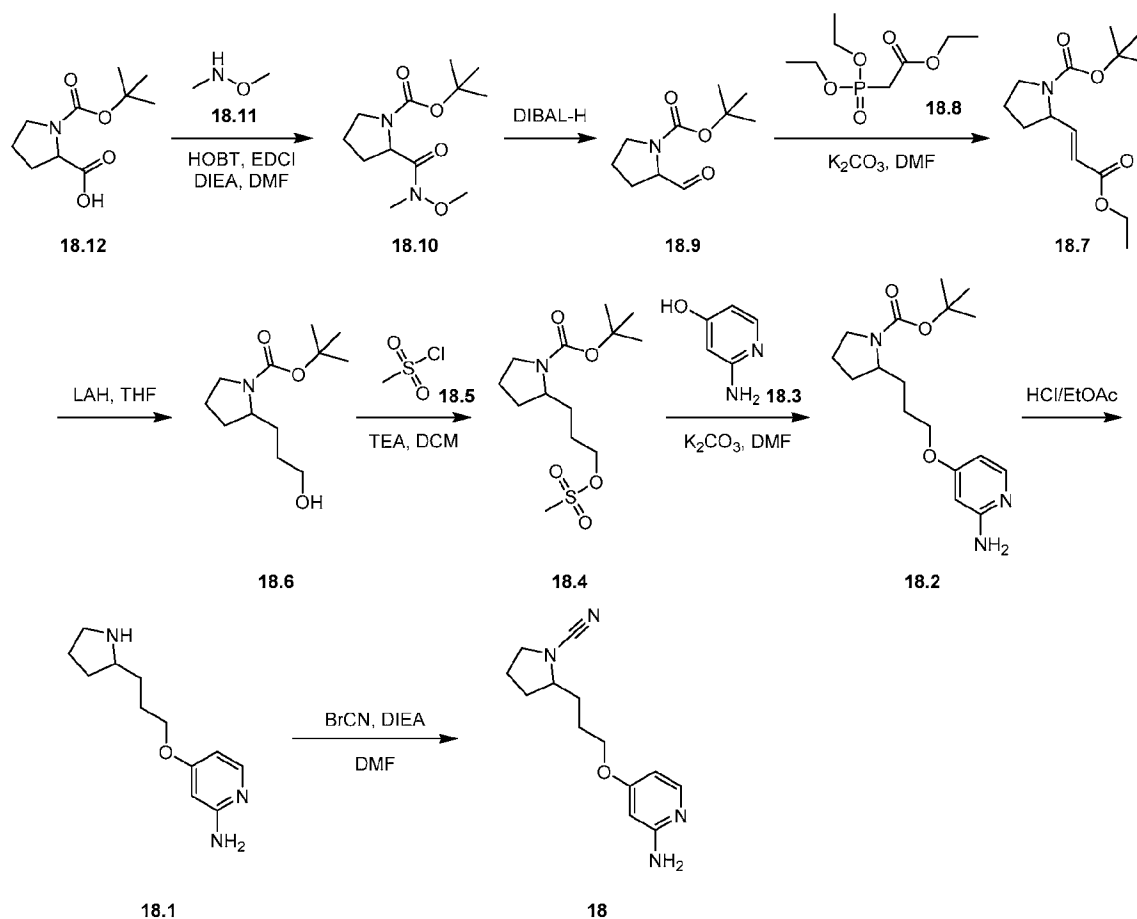
- 25 **[0268]** To a solution of compound **17.3a** (149.75 mg, 1.36 mmol, 1 *eq*) in ACN (7 mL) was added K₂CO₃ (375.93 mg, 2.72 mmol, 2 *eq*) and compound **17.3** (400 mg, 1.36 mmol, 1 *eq*) at 25°C under N₂. The resulting mixture was stirred at 80°C for 16 hours. The reaction mixture was added water (5 mL), extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine (10 mL x 1), dried over Na₂SO₄, filtered and concentrated
30 under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 100:1 to 5:1). Compound **17.2** (200 mg, 650.64 µmol, 47.84% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-d) ppm

1.47 - 1.58 (m, 11 H) 1.84 - 1.89 (m, 2 H) 2.04 - 2.06 (m, 1 H) 2.34 (m, 1 H) 2.93 - 2.98 (m, 1 H) 3.27 - 3.66 (m, 3 H) 3.97 - 4 (m, 2 H) 4.40 (s, 2 H) 5.97 (s, 1 H) 6.25 (d, J=5.6 Hz, 1 H) 7.90 (d, J=5.6 Hz, 1 H)

- [0269] A solution of compound **17.2** (200 mg, 650.64 μ mol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25°C for 1h. The reaction mixture was concentrated under reduced pressure to give a residue. Compound **17.1** (90 mg, 321.21 μ mol, 49.37% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-d₄) ppm 1.73 - 1.77 (m, 1 H) 2.02 - 2.03 (m, 2 H) 2.26 - 2.65 (m, 1 H) 2.52 - 2.54 (m, 1 H) 2.94 - 2.97 (m, 1 H) 3.42 - 3.61 (m, 4 H) 4.22 - 4.26 (m, 2 H) 6.41 (d, J=2.4 Hz, 1 H) 6.54 (dd, J=7.2 Hz, 2.0 Hz, 1 H) 7.90 (d, J=7.6 Hz, 1 H).
- [0270] To a solution of compound **17.1** (90 mg, 321.21 μ mol, 1 *eq*) in DMF (3 mL) was added DIEA (166.05 mg, 1.28 mmol, 224.39 μ L, 4 *eq*) and BrCN (34.02 mg, 321.21 μ mol, 23.63 μ L, 1 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 0°C for 1 hour. The reaction mixture was added water 10 mL, extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition). Product **17** (10 mg, 43.05 μ mol, 13.40% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₂H₁₆N₄O:232; found 233; RT=1.506 min. ¹H NMR (400 MHz, chloroform-d) ppm 1.47 - 1.67 (m, 1 H) 1.86 - 1.90 (m, 2 H) 2.11 - 2.13 (m, 1 H) 2.35 - 2.46 (m, 1 H) 3.10 - 3.12 (m, 1 H) 3.40 - 3.61 (m, 3 H) 3.97 - 4.01 (m, 2 H) 4.40 (s, 2 H) 5.95 (d, J=2.0 Hz, 1 H) 6.23 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.91 (d, J=5.6 Hz, 1 H).

Example 18. Preparation of 2-(3-((2-aminopyridin-4-yl)oxy)propyl)pyrrolidine-1-carbonitrile (18)

- [0271] To a mixture of compound **18.12** (20 g, 92.92 mmol, 1 *eq*), EDCI (17.81 g, 92.92 mmol, 1 *eq*) and HOBt (12.55 g, 92.92 mmol, 1 *eq*) in DMF (200 mL) was added DIEA (48 g, 92.92 mmol, 1 *eq*) and compound **18.11** (9.06 g, 92.92 mmol, 1 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 2 hours. The aqueous phase was extracted with EtOAc (50mLx3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1). Compound **18.10** (19.60 g, 75.88 mmol, 81.66% yield) was obtained as a black brown oil.



[0272] To a solution of compound **18.10** (10 g, 38.71 mmol, 1 *eq*) in THF (200 mL) was added DIBAL-H (6.01 g, 42.58 mmol, 1.10 *eq*) in one portion at -78 °C under N₂. The mixture was stirred at -78 °C for 2 hours. After the reaction mixture was cooled to 0 °C, the reaction mixture was quenched by addition of 100 mL of H₂O, followed by 15 mL of 15% aqueous NaOH. After being stirred at room temperature for 10 min, the solid was removed by filtration. The filtrate was concentrated to dryness to give crude product. Compound **18.9** (6.70 g, crude) was obtained as colorless oil.

[0273] To a mixture of compound **18.8** (4.69 g, 20.91 mmol, 4.15 mL, 1 *eq*) and K₂CO₃ (7.23 g, 52.27 mmol, 2.50 *eq*) in DMF (100 mL) was added compound **18.9** (5 g, 25.09 mmol, 1.20 *eq*) in one portion at 20 °C under N₂. The mixture was stirred at 50 °C for 15 hours. The aqueous phase was extracted with ethyl acetate (50 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1). Compound **18.7** (3.20 g, 11.88 mmol, 56.82% yield) was obtained as a colorless oil.

[0274] To a solution of compound **18.7** (2 g, 7.43 mmol, 1 *eq*) in THF (30 mL) was added LAH (1.41 g, 37.15 mmol, 5 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 15 min. After the reaction mixture was cooled to 0 °C, the reaction mixture was quenched by addition of 5 mL of H₂O, followed by 2 mL of 15% aqueous NaOH. After being stirred at room temperature for 10 min, the solid was removed by filtration. The filtrate was concentrated to dryness to give crude product. The residue was purified by prep-TLC (SiO₂, PE: ethyl acetate = 2:1). Compound **18.6** (1.08 g, 4.71 mmol, 63.39% yield) was obtained as a colorless oil. LCMS (ESI): m/z: [M + H] called for C₁₂H₂₃NO₃: 230; found 230; RT=0.741 min.

[0275] To a mixture of compound **18.6** (300 mg, 1.31 mmol, 1 *eq*) and TEA (198.84 mg, 1.96 mmol, 272.38 µL, 1.50 *eq*) in DCM (10 mL) was added compound **18.5** (180.07 mg, 1.57 mmol, 121.67 µL, 1.20 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 15 min. The aqueous phase was extracted with ethyl acetate (30mLx3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. Compound **18.4** (600 mg, crude) was obtained as light yellow oil.

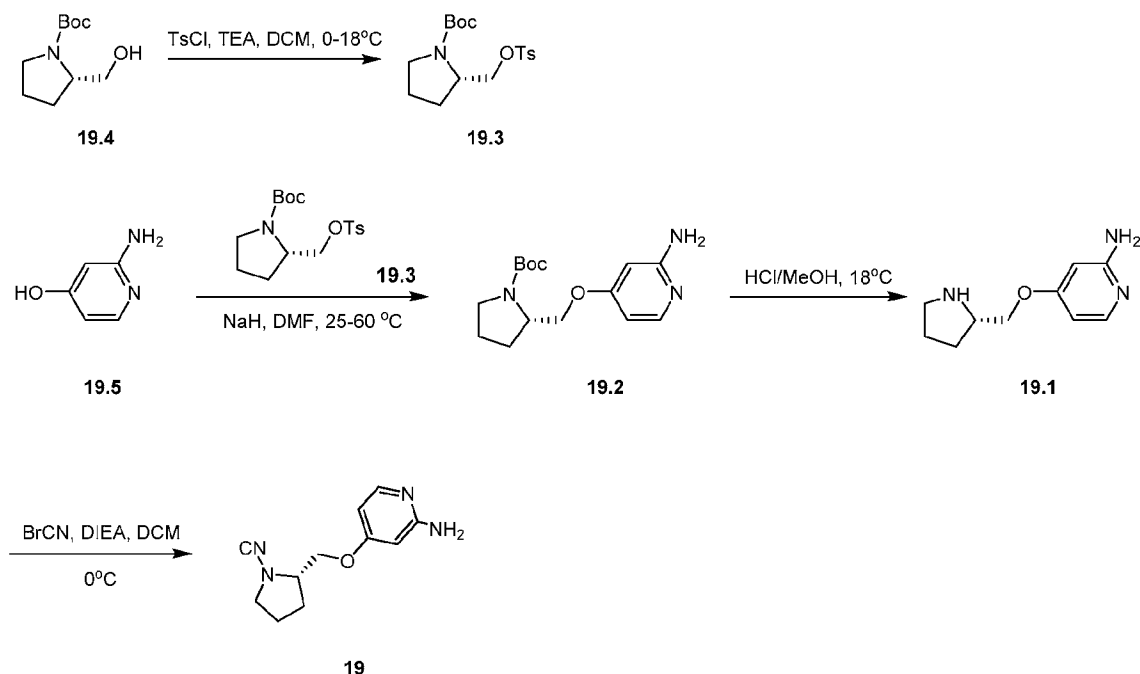
[0276] To a mixture of compound **18.4** (600 mg, 1.95 mmol, 1 *eq*) and compound **18.3** (214.91 mg, 1.95 mmol, 1 *eq*) in DMF (5 mL) was added K₂CO₃ (539.51 mg, 3.90 mmol, 2 *eq*) in one portion at 15°C under N₂. The mixture was stirred at 65 °C for 15 hours. The aqueous phase was extracted with ethyl acetate (30mLx3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. Compound **18.2** (50 mg, 155.56 µmol, 7.98% yield) was obtained as colorless oil.

[0277] A mixture of compound **18.2** (50 mg, 155.56 µmol, 1 *eq*) in HCl/EtOAc (4 M, 10 mL, 257.14 *eq*), the mixture was stirred at 15 °C for 15 hours. Then the mixture was concentrated in vacuum. Compound **18.1** (50 mg, crude) was obtained as a white solid. LCMS (ESI): m/z: [M + H] called for C₁₂H₁₉N₃O: 220; found 220; RT=0.114 min.

[0278] To a mixture of compound **18.1** (50 mg, 225.94 µmol, 1 *eq*) and DIEA (58.40 mg, 451.88 µmol, 78.92 µL, 2 *eq*) in DMF (2 mL) was added carbononitridic bromide (23.93 mg, 225.94 µmol, 16.62 µL, 1 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 15 °C for 15 hours. The aqueous phase was extracted with ethyl acetate (30mLx3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (basic

condition). Product **18** (1.20 mg, 4.87 μ mol, 2.16% yield) was obtained as a white solid. ^1H NMR (400 MHz, chloroform-*d*) δ ppm 1.35 - 1.75 (m, 5 H) 1.77 - 2.01 (m, 6 H) 2.02 - 2.21 (m, 2 H) 3.33 - 3.54 (m, 2 H) 3.62 (br d, $J=6.15$ Hz, 2 H) 3.88 - 4.10 (m, 2 H) 4.41 (br s, 2 H) 5.98 (s, 1 H) 6.14 - 6.37 (m, 1 H) 7.76 - 8.02 (m, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}$: 247; found 247; $\text{RT}=1.044$ min.

Example 19. Preparation of (*S*)-2-(((2-aminopyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (19**)**



[0279] To a mixture of compound **19.4** (1 g, 4.97 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (1.14 g, 5.96 mmol, 1.20 *eq*) in DCM (15 mL) was added DMAP (97.12 mg, 794.99 μ mol, 0.16 *eq*) and TEA (754.17 mg, 7.45 mmol, 1.03 mL, 1.50 *eq*) in one portion at 0°C under N_2 . The mixture was then heated to 18°C and stirred for 10 hours. The reaction mixture was diluted with H_2O 20 mL and extracted with EtOAc 45 mL (15 mL \times 3). The combined organic layers were washed with brine 20 mL (20 mL \times 1), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give compound **19.3** (1.70 g, crude) as a colorless oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{17}\text{H}_{25}\text{NSO}_5$: 355; found 300; $\text{RT}=0.890$ min.

[0280] To a solution of compound **19.5** (579.28 mg, 5.26 mmol, 1.10 *eq*) in DMF (20 mL) was added NaH (172.18 mg, 7.17 mmol, 1.50 *eq*) portionwise at 25°C under N_2 . The mixture was stirred at 25°C for 30 mins, then was added compound **19.3** (1.70 g, 4.78 mmol, 1 *eq*).

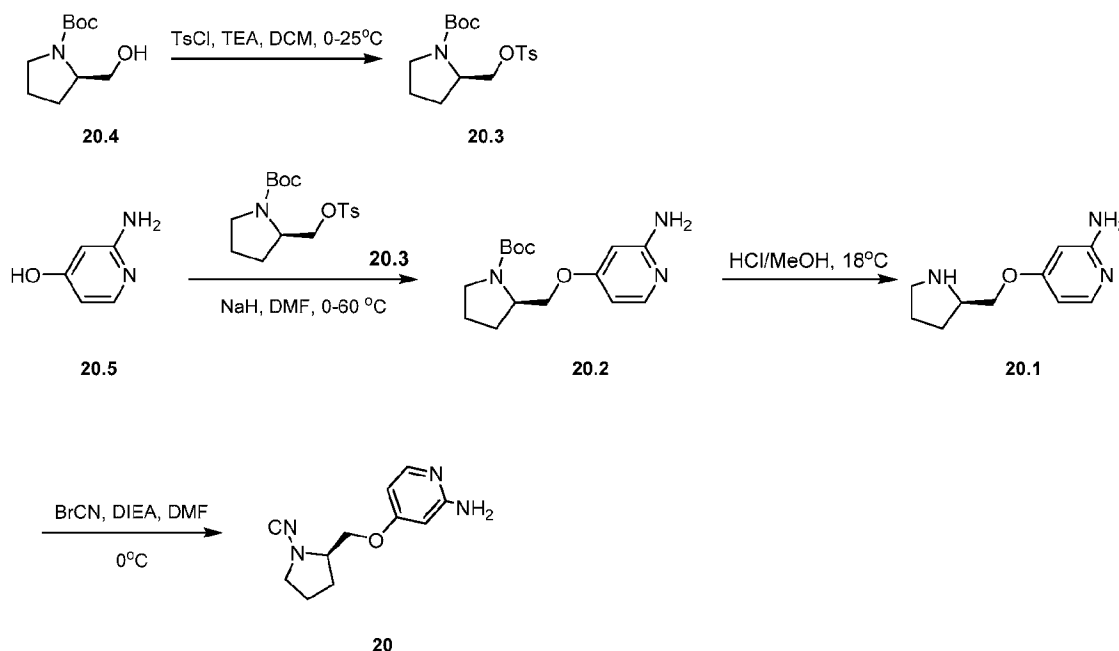
The mixture was heated to 60 °C and stirred for 9.5 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column

5 chromatography (SiO₂, DCM:MeOH=20:1) to give compound **19.2** (700 mg, 2.39 mmol, 49.92% yield) as a colorless oil. LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 293; found 294; RT=0.667 min.

[0281] Compound **19.2** (700 mg, 2.39 mmol, 1 eq) was added into a solution of HCl/MeOH (10 mL). The mixture was stirred at 18 °C for 15 hours. The reaction mixture
10 was concentrated under reduced pressure to give compound **19.1** (550 mg, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.74 (dq, *J*=12.66, 8.20 Hz, 1 H) 1.83 - 2.05 (m, 2 H) 2.06 - 2.18 (m, 1 H) 3.14 - 3.28 (m, 2 H) 3.67 (br s, 1 H) 3.87 - 3.99 (m, 1 H) 4.40 (d, *J*=5.90 Hz, 2 H) 6.43 (d, *J*=2.51 Hz, 1 H) 6.54 (dd, *J*=7.28, 2.51 Hz, 1 H) 7.92 (d, *J*=7.28 Hz, 1 H) 8.04 (br s, 2 H).

[0282] To a mixture of compound **19.1** (200 mg, 1.03 mmol, 1 eq) and DIEA (532.47 mg, 4.12 mmol, 719.55 μL, 4 eq) in DCM (3 mL) was added carbononitridic bromide (109.10 mg, 1.03 mmol, 75.76 μL, 1 eq) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins. The reaction mixture diluted with H₂O 3 mL and extracted with DCM 9 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried
20 over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **19** (30 mg, 137.46 μmol, 13.35% yield) as a yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O: 218; found 219; RT=1.953 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.72 (dq, *J*=12.27, 6.16 Hz, 1 H) 1.82 - 1.96 (m, 2 H) 1.99 - 2.09 (m, 1 H) 3.36 - 3.49 (m, 2 H) 3.89 - 4 (m, 2 H) 4 - 4.07 (m, 1
25 H) 5.81 (s, 2 H) 5.97 (d, *J*=2.13 Hz, 1 H) 6.14 (dd, *J*=5.77, 2.26 Hz, 1 H) 7.74 (d, *J*=5.77 Hz, 1 H).

Example 20. Preparation of (*R*)-2-(((2-aminopyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (20)



- [0283] To a mixture of compound **20.4** (1 g, 4.97 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (1.14 g, 5.96 mmol, 1.20 *eq*) in DCM (15 mL) was added DMAP (97.12 mg, 794.99 μ mol, 0.16 *eq*) and TEA (754.17 mg, 7.45 mmol, 1.03 mL, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was then heated to 25 °C and stirred for 10 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 15 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **20.3** (1.90 g, crude) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) ppm 1.30 - 1.48 (m, 9 H) 1.71 - 2.02 (m, 4 H) 2.39 - 2.51 (m, 3 H) 3.21 - 3.42 (m, 2 H) 3.80 - 4.03 (m, 1 H) 4.09 (d, J=6.15 Hz, 1 H) 7.35 (d, J=4.77 Hz, 2 H) 7.78 (d, J=8.16 Hz, 2 H). LCMS (ESI): m/z: [M + H] calcd for C₁₇H₂₅NSO₅: 355; found 256,300; RT=1.119 min.
- [0284] To a solution of compound **20.5** (647.43 mg, 5.88 mmol, 1.10 *eq*) in DMF (20 mL) was added NaH (192.43 mg, 8.02 mmol, 1.50 *eq*) portionwise at 0°C under N₂. The mixture was stirred at 0°C for 30 mins, then was added compound **20.3** (1.90 g, 5.35 mmol, 1 *eq*). The mixture was heated to 60 °C and stirred for 9.5 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 15 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Then the residue was purified by column (SiO₂,

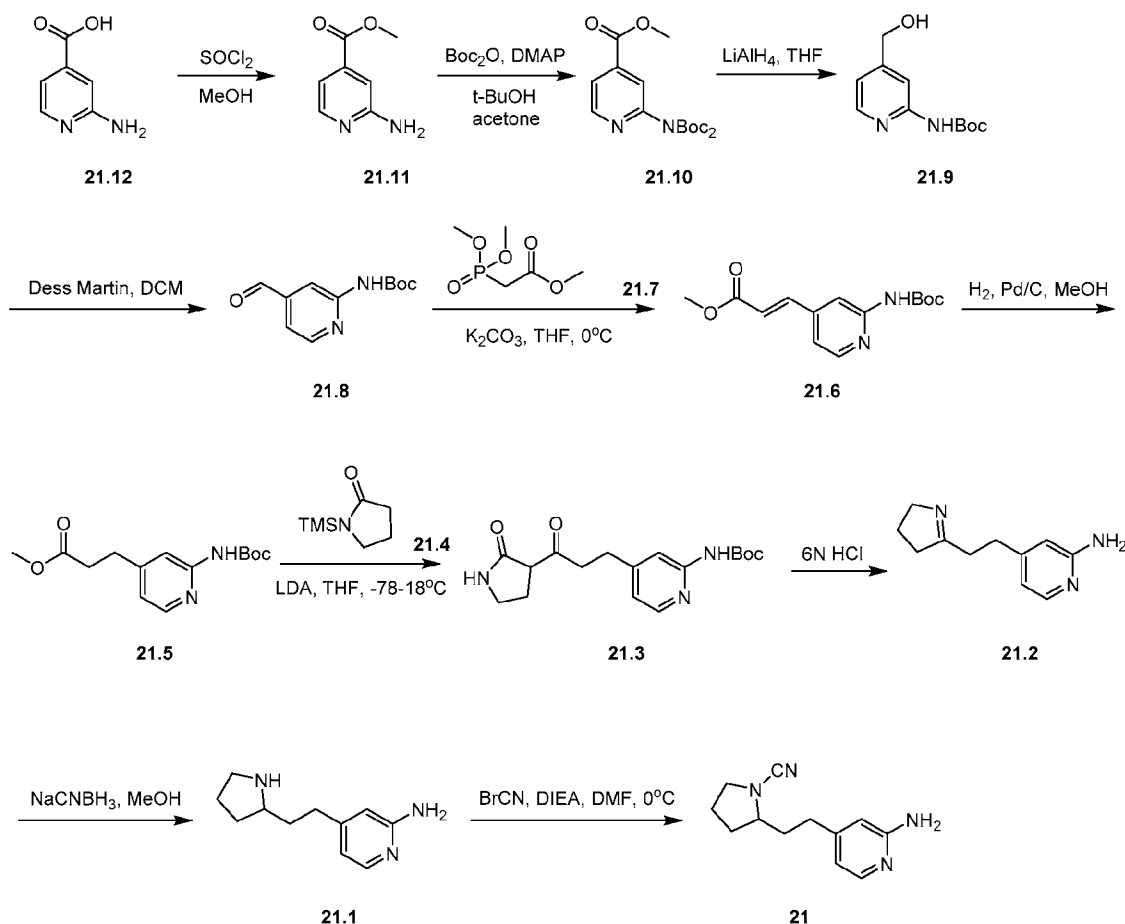
DCM/MeOH=10:1) to give compound **20.2** (900 mg, 3.07 mmol, 57.34% yield) as a yellow oil. ¹H NMR (400 MHz, methanol-d₄) ppm 1.82 - 1.93 (m, 1 H) 1.95 - 2.08 (m, 3 H) 3.36 - 3.41 (m, 2 H) 3.90 - 4.02 (m, 1 H) 4.04 - 4.20 (m, 2 H) 6.12 (d, J=15.94 Hz, 1 H) 6.26 (dd, J=6.09, 2.32 Hz, 1 H) 7.64 - 7.76 (m, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 293; found 294; RT=0.671 min.

[0285] Compound **20.2** (900 mg, 3.07 mmol, 1 eq) was added into a solution of HCl/MeOH (10 mL). The mixture was stirred at 18 °C for 15 hours. The reaction mixture was concentrated under reduced pressure to give compound **20.1** (900 mg, crude) as a yellow solid. ¹H NMR (400 MHz, methanol-d₄) ppm 1.84 - 1.96 (m, 1 H) 1.98 - 2.20 (m, 2 H) 2.21 - 2.35 (m, 1 H) 3.27 (dt, J=3.20, 1.71 Hz, 1 H) 3.33 - 3.41 (m, 2 H) 4.28 - 4.41 (m, 1 H) 4.49 (dd, J=11.03, 3.53 Hz, 1 H) 6.46 (d, J=2.21 Hz, 1 H) 6.58 (dd, J=7.28, 2.43 Hz, 1 H) 7.70 - 7.82 (m, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₅N₃O: 193; found 194; RT=0.086 min.

[0286] To a mixture of compound **20.1** (200 mg, 1.03 mmol, 1 eq) and DIEA (532.47 mg, 4.12 mmol, 719.55 µL, 4 eq) in DCM (3 mL) was added carbononitridic bromide (109.10 mg, 1.03 mmol, 75.76 µL, 1 eq) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 30 mins. The reaction mixture diluted with H₂O 3 mL and extracted with DCM 3 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **20** (100 mg, 458.19 µmol, 44.48% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 1.71 (dq, J=12.23, 6.17 Hz, 1 H) 1.79 - 1.96 (m, 2 H) 1.97 - 2.11 (m, 1 H) 3.35 - 3.49 (m, 2 H) 3.89 - 4 (m, 2 H) 4 - 4.08 (m, 1 H) 5.93 (s, 1 H) 5.99 (d, J=2.26 Hz, 1 H) 6.11 - 6.20 (m, 1 H) 7.74 (d, J=6.02 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O: 218; found 219; RT=1.981 min.

Example 21. Preparation of 2-(2-(2-aminopyridin-4-yl)ethyl)pyrrolidine-1-carbonitrile (21)

[0287] To a solution of compound **21.12** (58 g, 419.92 mmol, 1 eq) in MeOH (600 mL) was added SOCl₂ (99.92 g, 839.84 mmol, 60.93 mL, 2 eq) dropwise at 0 °C under N₂. The mixture was stirred at 0 °C for 30 mins, then was heated to 18 °C and stirred at 18 °C for 14.5 hours. The reaction mixture was concentrated under reduced pressure to give compound **21.11** (65 g, crude) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₈N₂O₂: 152; found 153; RT=0.100 min.



- [0288] To a mixture of compound **21.11** (65 g, 427.21 mmol, 1 *eq*) and DMAP (2.61 g, 21.36 mmol, 0.05 *eq*) in t-BuOH (500 mL) and acetone (150 mL) was added Boc_2O (279.72 g, 1.28 mol, 294.44 mL, 3 *eq*) dropwies at 18°C under N_2 . The mixture was stirred at 18°C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to obtain compound **21.10** (110 g, 312.16 mmol, 73.07% yield) as a white solid. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_6$: 352; found 353; $\text{RT}=0.877$ min. ^1H NMR (400 MHz, chloroform-*d*) δ ppm 1.39 - 1.50 (m, 19 H) 3.97 (s, 3 H) 7.77 (dd, $J=5.02$, 1.38 Hz, 1 H) 7.82 (s, 1 H) 8.62 (d, $J=5.02$ Hz, 1 H)
- [0289] To a solution of compound **21.10** (60 g, 170.27 mmol, 1 *eq*) in THF (1 L) was added LiAlH_4 (12.92 g, 340.54 mmol, 2 *eq*) portionwise at 0°C under N_2 . The mixture was stirred at 0°C for 1 hours, then heated to 18°C and stirred at 18°C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H_2O 1000 mL and extracted with EtOAc 1500 mL (500 mL x 3). The combined organic layers were washed with brine 1000 mL (1000 mL x 1), 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/Ethyl acetate=2:1) to give compound **21.9** (15 g, 66.89 mmol, 39.28% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₆N₂O₃: 293; found 294; RT=0.313 min.

[0290] To a solution of compound **21.9** (8 g, 35.67 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (18.16 g, 42.81 mmol, 13.25 mL, 1.20 *eq*) portionwise at 18°C under N₂. The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O 60 mL and extracted with DCM 150 mL (50 mL x 3). The combined organic layers were washed with brine 100 mL (100 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **21.8** (5.10 g, 22.95 mmol, 64.33% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₂O₃: 222; found 223; RT=0.313 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.59 (s, 9 H) 7.41 (dd, *J*=5.08, 1.32 Hz, 1 H) 8.48 (s, 1 H) 8.52 (d, *J*=5.15 Hz, 1 H) 8.83 (br s, 1 H).

[0291] To a mixture of compound **21.8** (2.50 g, 11.25 mmol, 1 *eq*) and methyl 2-dimethoxyphosphorylacetate **21.7** (2.05 g, 11.25 mmol, 1.63 mL, 1 *eq*) in THF (30 mL) was added K₂CO₃ (3.11 g, 22.50 mmol, 2 *eq*) in one portion at 50°C under N₂. The mixture was stirred at 50 °C for 15 hours. The reaction mixture was diluted with H₂O 30 mL and extracted with EtOAc 90 mL (30 mL x 3). The combined organic layers were washed with brine 50 mL (50 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **21.6** (2.40 g, 8.62 mmol, 76.62% yield) as a white solid.

[0292] LCMS (ESI): m/z: [M + H] calcd for C₁₄H₁₈N₂O₄: 278; found 279; RT=0.739 min.

[0293] To a solution of compound **21.6** (1.40 g, 5.03 mmol, 1 *eq*) in MeOH (100 mL) was added Pd-C (10%, 0.2 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50psi) at 20°C for 15 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **21.5** (1.30 g, 4.64 mmol, 92.20% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₄H₂₀N₂O₄: 280; found 281; RT=0.617 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.47 (s, 9 H) 2.59 (t, *J*=7.78 Hz, 2 H) 2.78 - 2.98 (m, 2 H) 3.50 - 3.71 (m, 3 H) 6.66 - 6.82 (m, 1 H) 7.79 (s, 1 H) 8.13 (d, *J*=5.15 Hz, 1 H) 8.83 (s, 1 H)

[0294] To a solution of DIPA (505.95 mg, 5 mmol, 702.71 μ L, 2 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 1.50 mL, 1.50 *eq*) dropwise at -78°C under N₂. The mixture was then added compound **21.4** (589.84 mg, 3.75 mmol, 601.88 μ L, 1.50 *eq*) in one portion at -78°C, the mixture was stirred at -78°C for 30 mins, then was added compound **21.5** (700 mg, 2.50 mmol, 1 *eq*) in one portion at -78°C, the mixture was heated to 18 °C and stirred for 14.5 hours. The reaction mixture was quenched by addition H₂O 10 mL and then diluted with EtOAc 5 mL and extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, PE: EA = 2:1) to give compound **21.3** (180 mg, 539.92 μ mol, 21.60% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₇H₂₃N₃O₄: 333; found 334; RT=0.597 min.

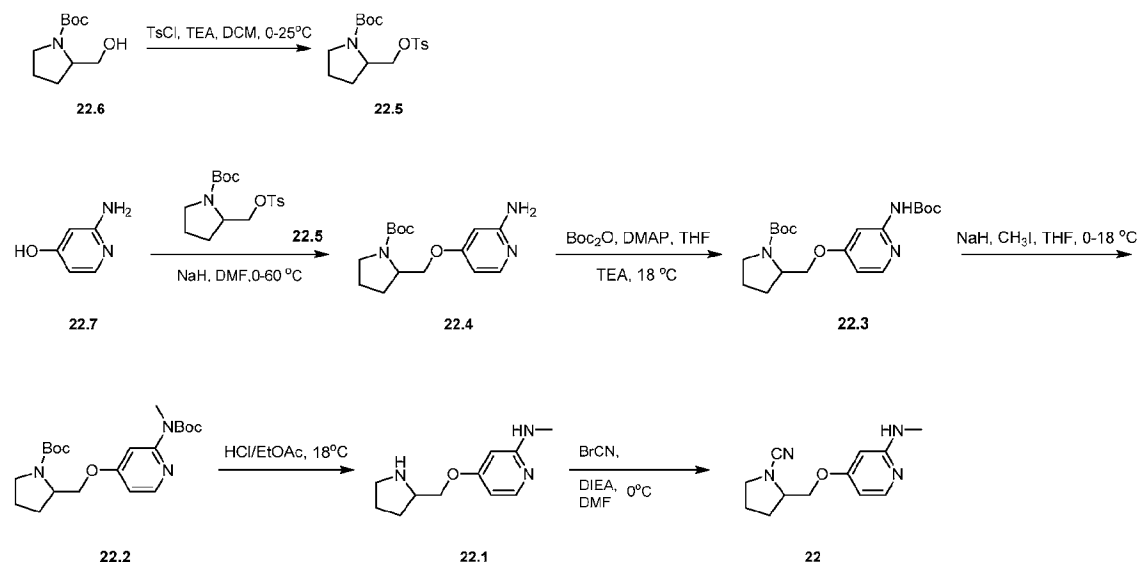
[0295] Compound **21.3** (180 mg, 539.92 μ mol, 1 *eq*) was mixed with 6 N HCl (5 mL), heated at 100°C for 15 hours. The mixture was concentrated at reduced pressure to a syrup and then basified with 10 % KOH(10 ml), the resulting two phase mixture was extracted with EtOAc 15 ml (5 ml x 3) and the extract dry Na₂SO₄ and concentrated to give compound **21.2** (90 mg, crude) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₆H₂₃N₃O₂: 189; found 190; RT=0.097 min.

[0296] To a mixture of compound **21.2** (90 mg, 475.54 μ mol, 1 *eq*) and NaBH₃CN (44.82 mg, 713.30 μ mol, 1.50 *eq*) in MeOH (1 mL) was added HCl/MeOH (500 μ L) in one portion at 18°C under N₂. The mixture was stirred at 18 °C for 4 hours. The reaction mixture was concentrated under reduced pressure to give a residue, then was diluted with H₂O 2 mL and extracted with EtOAc 6 mL (2 mL x 3). The combined organic layers were washed with brine 5 mL (5 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **21.1** (90 mg, 470.54 μ mol, 98.95% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₇N₃: 191; found 192; RT=0.095 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.27 - 1.39 (m, 2 H) 1.64 - 1.85 (m, 4 H) 1.88 - 1.99 (m, 1 H) 2.43 - 2.59 (m, 2 H) 2.78 - 2.88 (m, 1 H) 2.93 - 3.04 (m, 2 H) 5.86 (s, 2 H) 6.38 (s, 1 H) 6.46 (dd, *J*=5.29, 1.32 Hz, 1 H) 7.89 (d, *J*=5.07 Hz, 1 H).

[0297] To a mixture of compound **21.1** (40 mg, 209.13 μ mol, 1 *eq*) and DIEA (108.11 mg, 836.51 μ mol, 146.10 μ L, 4 *eq*) in DMF (1 mL) was added carbononitridic bromide (22.15 mg, 209.13 μ mol, 15.38 μ L, 1 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins. The residue was purified by prep-HPLC (neutral condition) to give product

21 (5 mg, 23.12 μ mol, 11.05% yield) as a white solid. LCMS (ESI): m/z : $[M + H]^+$ calcd for $C_{12}H_{16}N_4$: 216; found 217; RT=2.153 min. 1H NMR (400 MHz, DMSO- d_6) δ ppm 1.48 - 1.60 (m, 1 H) 1.60 - 1.70 (m, 1 H) 1.76 - 1.93 (m, 3 H) 1.94 - 2.04 (m, 1 H) 2.42 - 2.47 (m, 2 H) 3.35 - 3.44 (m, 2 H) 3.48 - 3.57 (m, 1 H) 5.77 (s, 2 H) 6.28 (s, 1 H) 6.33 - 6.40 (m, 1 H) 7.78 (d, $J=5.15$ Hz, 1 H).

Example 22. Preparation of 2-(((2-(methylamino)pyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (22)



[0298] To a mixture of compound **22.6** (4.50 g, 22.36 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (5.12 g, 26.83 mmol, 1.20 *eq*) in DCM (15 mL) was added DMAP (437.06 mg, 3.58 mmol, 0.16 *eq*) and TEA (3.39 g, 33.54 mmol, 4.65 mL, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was then heated to 25 °C and stirred for 10 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 15 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **22.5** (8 g, crude) as a colorless oil. 1H NMR (400 MHz, chloroform- d) δ ppm 1.20 - 1.52 (m, 9 H) 1.81 (br. s., 1 H) 1.93 (br. s., 2 H) 2.39 - 2.54 (m, 3 H) 3.17 - 3.44 (m, 2 H) 3.80 - 4.04 (m, 1 H) 4.10 (d, $J=6.02$ Hz, 1 H) 7.30 - 7.42 (m, 2 H) 7.67 - 7.86 (m, 2 H).

[0299] To a solution of compound **22.7** (2.73 g, 24.76 mmol, 1.10 *eq*) in DMF (20 mL) was added NaH (810.24 mg, 33.76 mmol, 1.50 *eq*) portionwise at 0°C under N₂. The mixture was stirred at 0°C for 30 mins, then was added compound **22.5** (8 g, 22.51 mmol, 1 *eq*). The mixture was heated to 60 °C and stirred for 9.5 hours. The reaction mixture was diluted with

H₂O 20 mL and extracted with EA 15 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM:MeOH=20:1) to give compound **22.4** (4 g, 13.64 mmol, 60.57% yield) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) δ ppm 1.40 - 1.57 (m, 9 H) 1.78 - 2.05 (m, 4 H) 3.37 (d, J=19.07 Hz, 2 H) 3.66 - 4 (m, 1 H) 4.12 (dd, J=14.05, 7.03 Hz, 2 H) 4.38 (br. s., 2 H) 5.89 - 6.15 (m, 1 H) 6.28 (d, J=4.02 Hz, 1 H) 7.88 (br. s., 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 293; found 294; RT=0.681 min.

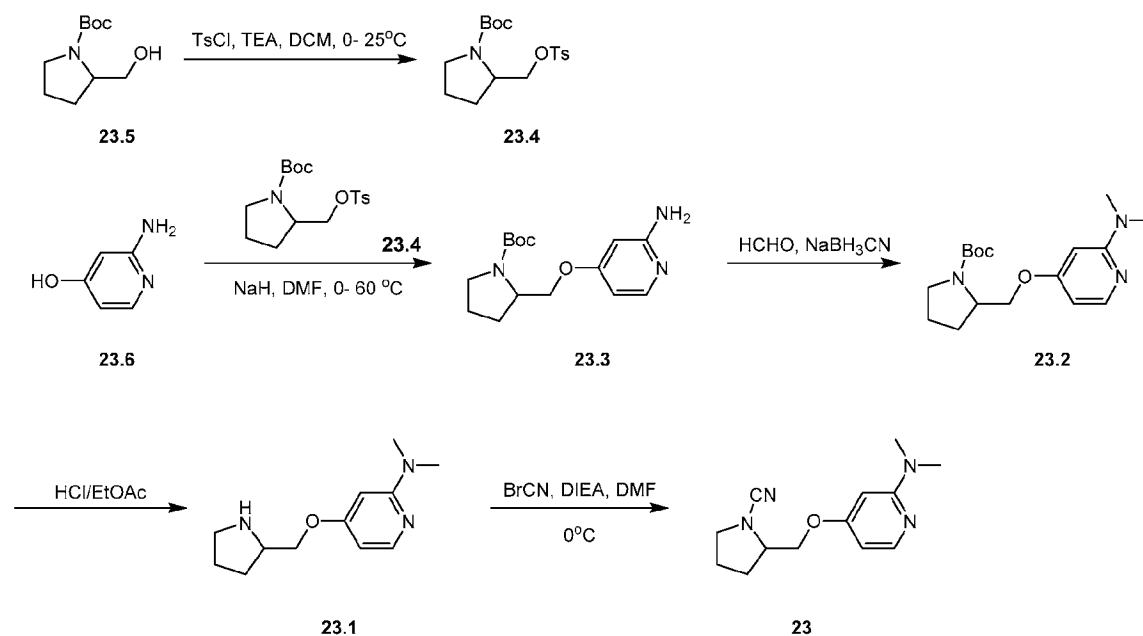
[0300] To a mixture of compound **22.4** (800 mg, 2.73 mmol, 1 eq) and TEA (828.75 mg, 8.19 mmol, 1.14 mL, 3 eq) in THF (10 mL) was added Boc₂O (714.99 mg, 3.28 mmol, 752.62 μL, 1.20 eq) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc 10 mL (10 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1) to give compound **22.3** (400 mg, 1.02 mmol, 37.24% yield) as a white solid. ¹H NMR (400 MHz, chloroform-d) δ ppm 1.47 (s, 9 H) 1.53 (s, 9 H) 1.86 (br. s., 1 H) 2 (br. s., 3 H) 3.21 - 3.55 (m, 2 H) 3.83 - 4.05 (m, 1 H) 4.13 (q, J=7.03 Hz, 4 H) 6.55 (br. s., 1 H) 7.52 (br. s., 1 H) 7.72 - 7.92 (m, 1 H) 8.05 (d, J=6.02 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₂₀H₃₁N₃O₅: 393; found 394; RT=0.764 min.

[0301] To a solution of compound **22.3** (210 mg, 533.70 μmol, 1 eq) in THF (5 mL) was added NaH (21.35 mg, 533.70 μmol, 60% purity, 1 eq) portionwise at 0 °C under N₂. The mixture was stirred at 0 °C for 30 mins, then the mixture was added CH₃I (75.75 mg, 533.70 μmol, 33.22 μL, 1 eq) dropwise at 0 °C, the mixture was heated to 18 °C and stirred for 1.5 hours. The reaction mixture was diluted with H₂O 2 mL and extracted with EtOAc 2 mL (2 mL x 3). The combined organic layers were washed with brine 5 mL (5 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1) to give compound **22.2** (160 mg, 392.64 μmol, 73.57% yield) as a colorless oil, Combined ET6889-326 and ET6889-329 to afford compound **10** (210 mg). LCMS (ESI): m/z: [M + H] calcd for C₂₁H₃₃N₃O₅: 407; found 408; RT=0.777, 0.813 min.

[0302] Compound **22.2** (210 mg, 515.34 μmol , 1 *eq*) was added into a solution of HCl/EtOAc (5 mL). The mixture was stirred at 18 °C for 15 hours. The reaction mixture was concentrated under reduced pressure to give compound **22.1** (200 mg, crude) as a yellow solid. LCMS (ESI): m/z : $[M + H]$ calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}$: 207; found 208; $\text{RT}=0.093, 0.191$ min.

[0303] To a mixture of compound **22.1** (100 mg, 356.90 μmol , 1 *eq*, 2HCl) and DIEA (184.50 mg, 1.43 mmol, 249.32 μL , 4 *eq*) in DMF (2 mL) was added carbononitridic bromide (30.24 mg, 285.52 μmol , 21 μL , 0.80 *eq*) in one portion at 0 °C under N_2 . The mixture was stirred at 0 °C for 30 mins. The reaction mixture diluted with H_2O 3 mL and extracted with DCM 3 mL (3 mL x 3). The combined organic layers were washed with brine 4 mL (4 mL x 1), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give product **22** (5 mg, 21.53 μmol , 6.03% yield) as a yellow solid. ^1H NMR (400 MHz, chloroform- d) δ ppm 1.85 - 2.07 (m, 3 H) 2.08 - 2.20 (m, 1 H) 2.90 (d, $J=5.27$ Hz, 3 H) 3.40 - 3.51 (m, 1 H) 3.51 - 3.60 (m, 1 H) 3.93 - 4.02 (m, 1 H) 4.02 - 4.09 (m, 2 H) 5.78 - 5.93 (m, 1 H) 6.20 (dd, $J=5.84, 2.07$ Hz, 1 H) 7.87 - 8 (m, 1 H). LCMS (ESI): m/z : $[M + H]$ calcd for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}$: 232; found 233; $\text{RT}=0.976$ min.

Example 23. Preparation of 2-(((2-(dimethylamino)pyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (23)



[0304] To a mixture of compound **23.5** (4.50 g, 22.36 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (5.12 g, 26.83 mmol, 1.20 *eq*) in DCM (15 mL) was added DMAP (437.06 mg, 3.58 mmol, 0.16 *eq*) and TEA (3.39 g, 33.54 mmol, 4.65 mL, 1.50 *eq*) in one portion at 0°C under N₂. The mixture was then heated to 25 °C and stirred for 10 hours.

5 The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **23.4** (8 g, crude) as a colorless oil. ¹H NMR (400 MHz, chloroform-d) δ ppm 1.20 - 1.52 (m, 9 H) 1.81 (br. s., 1 H) 1.93 (br. s., 2 H) 2.39 - 2.54 (m, 3 H) 3.17 - 3.44 (m, 2 H) 3.80 - 4.04 (m, 1 H) 4.10 (d, 10 J=6.02 Hz, 1 H) 7.30 - 7.42 (m, 2 H) 7.67 - 7.86 (m, 2 H).

[0305] To a solution of compound **23.4** (2.73 g, 24.76 mmol, 1.10 *eq*) in DMF (20 mL) was added NaH (810.24 mg, 33.76 mmol, 1.50 *eq*) portionwise at 0°C under N₂. The mixture was stirred at 0°C for 30 mins, then was added compound **23.6** (8 g, 22.51 mmol, 1 *eq*). The mixture was heated to 60 °C and stirred for 9.5 hours. The reaction mixture was diluted with 15 H₂O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM : MeOH=20:1) to give compound **23.3** (4 g, 13.64 mmol, 60.57% yield) as a yellow oil. ¹H NMR (400 MHz, chloroform-d) δ ppm 1.40 - 1.57 (m, 9 H) 1.78 - 2.05 (m, 4 20 H) 3.37 (d, J=19.07 Hz, 2 H) 3.66 - 4 (m, 1 H) 4.12 (dd, J=14.05, 7.03 Hz, 2 H) 4.38 (br. s., 2 H) 5.89 - 6.15 (m, 1 H) 6.28 (d, J=4.02 Hz, 1 H) 7.88 (br. s., 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 293; found 294; RT=0.681 min.

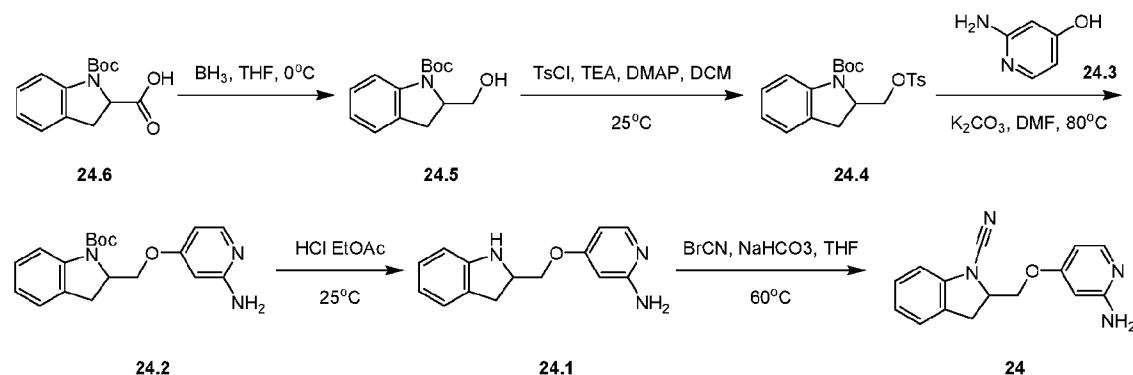
[0306] To a solution of compound **23.3** (100 mg, 340.88 μmol, 1 *eq*) in H₂O (250 μL) and ACETONITRILE (1 mL) was added HCHO (327 mg, 4.03 mmol, 300 μL, 37% purity, 11.82 25 *eq*) and NaBH₃CN (64.26 mg, 1.02 mmol, 3 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0°C for 30 mins, then was added CH₃COOH (21 mg, 349.71 μmol, 20 μL, 1.03 *eq*) dropwise at 0 °C, then heated to 18 °C and stirred for 1.5 hours. The reaction mixture was quenched by addition H₂O 5 mL then diluted with DCM 3 mL and extracted with DCM 3 mL (3 mL x 3). The combined organic layers were washed with brine 5 mL (5 30 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, DCM: MeOH = 10:1) to give

compound **23.2** (60 mg, 186.68 μmol , 54.76% yield) as a colorless oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_3$: 321; found 322; $\text{RT}=0.712$ min.

[0307] Compound **23.2** (60 mg, 186.67 μmol , 1 *eq*) was added into a solution of HCl/EtOAc (3 mL). The mixture was stirred at 18 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure to give compound **23.1** (60 mg, crude) as a yellow solid. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{12}\text{H}_{19}\text{N}_3\text{O}$: 221; found 222; $\text{RT}=0.096$ min.

[0308] To a mixture of compound **23.1** (60 mg, 232.77 μmol , 1 *eq*, HCl) and DIEA (120.34 mg, 931.08 μmol , 162.62 μL , 4 *eq*) in DMF (2 mL) was added carbononitridic bromide (24.65 mg, 232.77 μmol , 17.12 μL , 1 *eq*) in one portion at 0 °C under N_2 . The mixture was stirred at 0 °C for 30 mins. The residue was purified by prep-HPLC (neutral condition) to give product **23** (10 mg, 40.60 μmol , 17.44% yield) as a white solid. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}$: 246; found 247; $\text{RT}=2.441$ min. ^1H NMR (400 MHz, chloroform-*d*) δ ppm 1.91 - 2.08 (m, 3 H) 2.10 - 2.21 (m, 1 H) 3.10 (s, 6 H) 3.45 - 3.52 (m, 1 H) 3.54 - 3.61 (m, 1 H) 3.97 - 4.04 (m, 1 H) 4.04 - 4.11 (m, 2 H) 5.99 (d, $J=2.01$ Hz, 1 H) 6.19 (dd, $J=5.77$, 2.01 Hz, 1 H) 8.04 (d, $J=5.90$ Hz, 1 H)

Example 24. Preparation of 2-(((2-aminopyridin-4-yl)oxy)methyl)indoline-1-carbonitrile (**24**)



[0309] To a solution of compound **24.6** (950 mg, 3.61 mmol, 1 *eq*) in THF (15 mL) was added $\text{BH}_3\text{-Me}_2\text{S}$ (10 M, 721.64 μL , 2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H_2O 30 mL at 25 °C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with saturated brines (5 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **24.5** (750 mg, 3.01 mmol, 83.34% yield) was

obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₁₄H₁₉NO₃: 250; found 250; RT=0.800 min.

[0310] To a solution of compound **24.5** (750 mg, 3.01 mmol, 1 *eq*) in DCM (20 mL) was added TEA (1.52 g, 15.04 mmol, 2.09 mL, 5 *eq*) and TosCl (1.72 g, 9.03 mmol, 3 *eq*) and DMAP (183.77 mg, 1.50 mmol, 0.50 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C and extracted with DCM (50mL x 3). The combined organic layers were washed with saturated brines (15 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **24.4** (1.40 g, crude) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₂₁H₂₅NO₅S: 404; found 404; RT=0.925 min.

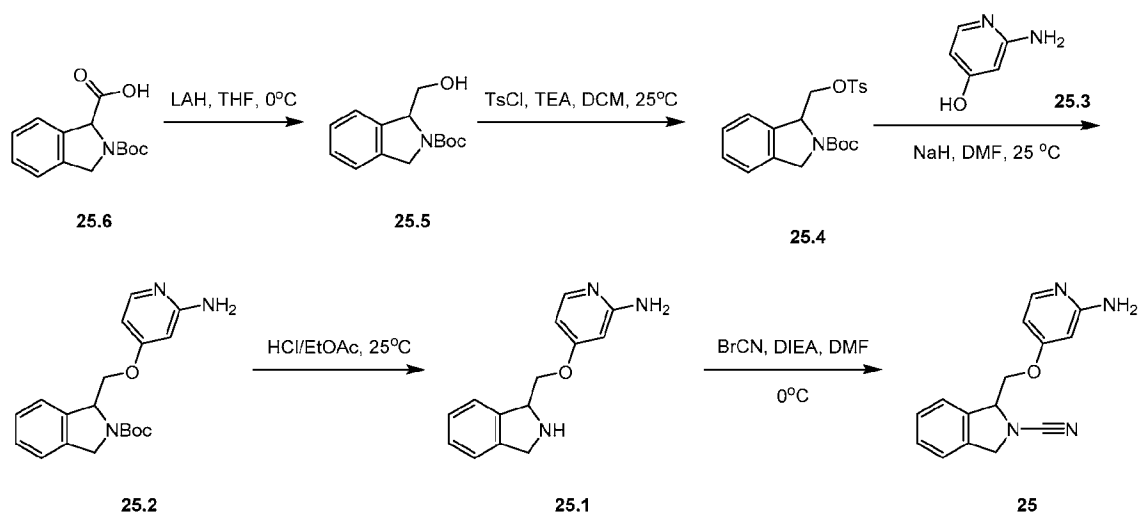
[0311] To a solution of compound **24.4** (1.40 g, 3.47 mmol, 1 *eq*) in DMF (30 mL) was added K₂CO₃ (959.10 mg, 6.94 mmol, 2 *eq*) and compound **24.3** (458.46 mg, 4.16 mmol, 1.20 *eq*). The mixture was stirred at 80 °C for 15 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (15 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **24.2** (200 mg, 585.82 µmol, 16.88% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.59 (s, 9 H) 2.46 (s, 1 H) 3.01 - 3.13 (m, 1 H) 3.35 (dd, *J*=16.25, 9.72 Hz, 1 H) 3.90 (br s, 1 H) 4.22 (br s, 1 H) 4.38 - 4.61 (m, 2 H) 4.79 (br s, 1 H) 6 (br s, 1 H) 6.22 - 6.31 (m, 1 H) 6.93 - 7.03 (m, 1 H) 7.14 - 7.23 (m, 2 H) 7.87 (d, *J*=5.77 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₉H₂₃N₃O₃: 342; found 342; RT=0.759 min.

[0312] A mixture of compound **24.2** (50 mg, 146.46 µmol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **24.1** (45 mg, 143.22 µmol, 97.79% yield, 2HCl) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₁₄H₁₅N₃O: 242; found 242; RT=0.129 min.

[0313] To a solution of compound **24.1** (40 mg, 127.30 µmol, 1 *eq*, 2HCl) in DMSO (2 mL) was added NaHCO₃ (53.47 mg, 636.52 µmol, 24.76 µL, 5 *eq*) and BrCN (13.48 mg, 127.30 µmol, 9.36 µL, 1 *eq*). The mixture was stirred at 60 °C for 2 hours. The residue was purified by prep-HPLC (TFA condition). Product **24** (1 mg, 3.76 µmol, 2.95% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 3.10 (dd, *J*=16.44, 5.90 Hz, 1 H) 3.51 (dd, *J*=16.44, 10.04 Hz, 1 H) 4.32 - 4.43 (m, 1 H) 4.45 - 4.54 (m, 1 H) 4.78 -

4.84 (m, 1 H) 6.39 (d, $J=2.51$ Hz, 1 H) 6.53 (dd, $J=7.28$, 2.38 Hz, 1 H) 6.93 (d, $J=8.03$ Hz, 1 H) 7.02 - 7.10 (m, 1 H) 7.26 (br d, $J=7.15$ Hz, 2 H) 7.73 (d, $J=7.28$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]^+$ called for $C_{15}H_{14}N_4O$: 267; found 267; RT=1.955 min.

Example 25. Preparation of 1-(((2-aminopyridin-4-yl)oxy)methyl)isoindoline-2-carbonitrile (25)



[0314] To a solution of compound **25.6** (800 mg, 3.04 mmol, 1 *eq*) in THF (8 mL) was added $BH_3 \cdot Me_2S$ (10 M, 608 μL , 2 *eq*) at 0°C. The mixture was stirred at 25°C for 15 hours. The reaction mixture was quenched by addition H_2O 20 mL at 25°C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **25.5** (600 mg, 2.41 mmol, 79.17% yield) was obtained as a yellow oil. LCMS (ESI): m/z : $[M + H]^+$ called for $C_{14}H_{19}NO_3$: 250; found 250; RT=0.752 min.

[0315] To a solution of compound **25.5** (100 mg, 401.11 μmol , 1 *eq*) in DCM (2 mL) was added TosCl (229.41 mg, 1.20 mmol, 3 *eq*) and TEA (202.94 mg, 2.01 mmol, 278 μL , 5 *eq*) and DMAP (14.70 mg, 120.33 μmol , 0.30 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H_2O 10 mL at 25°C and extracted with DCM (15 mL x 3). The combined organic layers were washed with saturated brines (5 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **25.4** (230 mg, crude) was obtained as a yellow oil. 1H NMR (400 MHz, chloroform-*d*) δ ppm 1.07 - 1.21 (m, 1 H) 1.32 - 1.42 (m, 2 H) 1.32 - 1.42 (m, 1 H) 1.44 - 1.55 (m, 8 H) 2.26 - 2.50 (m, 5 H) 3.02 - 3.36 (m, 1 H) 3.02 - 3.36 (m, 5 H) 4.15 -

4.81 (m, 4 H) 6.64 (d, $J=7.03$ Hz, 1 H) 7.11 - 7.41 (m, 8 H) 7.56 - 7.72 (m, 2 H) 7.83 (d, $J=8.16$ Hz, 1 H) 8.24 (d, $J=7.15$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]$ called for $C_{21}H_{25}NO_5S$: 404; found 404; RT=0.925 min.

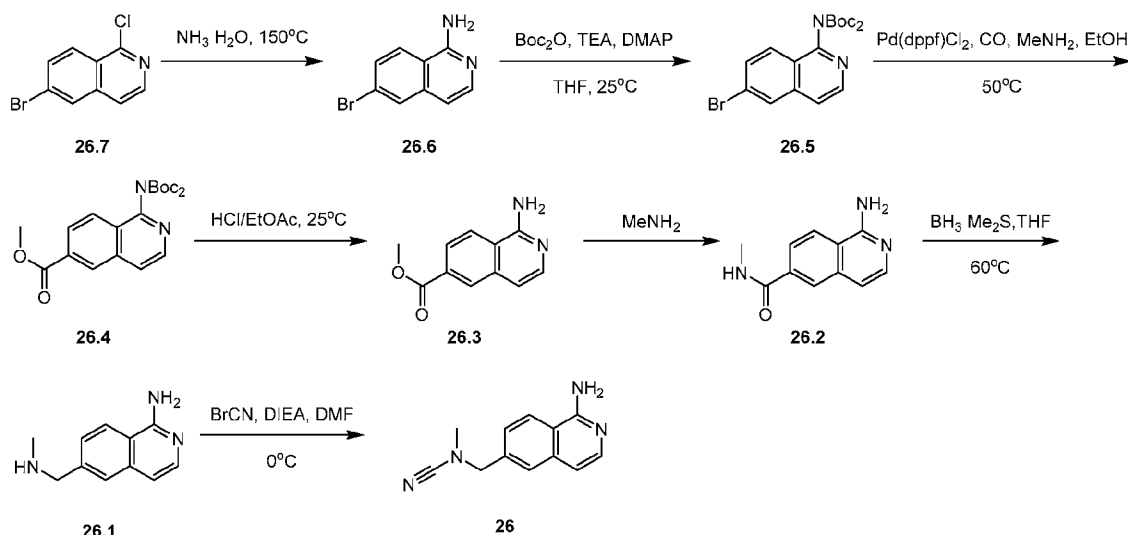
[0316] To a solution of compound **25.4** (230 mg, 570.03 μ mol, 1 *eq*) in DMF (3 mL) was added K_2CO_3 (157.57 mg, 1.14 mmol, 2 *eq*) and compound **25.3** (75.32 mg, 684.04 μ mol, 1.20 *eq*). The mixture was stirred at 80 °C for 15 hours. The reaction mixture was quenched by addition H_2O 10 mL at 25°C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with saturated brines (5 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , DCM: MeOH = 10:1). Compound **25.2** (50 mg, 146.46 μ mol, 25.69% yield) was obtained as a black brown oil. LCMS (ESI): m/z : $[M + H]$ called for $C_{19}H_{23}N_3O_3$: 342; found 342; RT=0.742 min.

[0317] A mixture of compound **25.2** (50 mg, 146.46 μ mol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **25.1** (30 mg, 95.48 μ mol, 65.19% yield, 2HCl) was obtained as a black brown oil. LCMS (ESI): m/z : $[M + H]$ called for $C_{14}H_{15}N_3O$: 242; found 242; RT=0.099 min.

[0318] To a solution of compound **25.1** (30 mg, 95.48 μ mol, 1 *eq*, 2HCl) in DMF (1 mL) was added DIEA (49.36 mg, 381.91 μ mol, 66.70 μ L, 4 *eq*) and BrCN (10.11 mg, 95.48 μ mol, 7.02 μ L, 1 *eq*). The mixture was stirred at 0 °C for 5 min. The residue was purified by prep-HPLC (basic condition). Product **25** (5 mg, 18.78 μ mol, 19.66% yield) was obtained as a white solid. 1H NMR (400 MHz, methanol- d_4) δ ppm 4.25 (dd, $J=10.36$, 5.95 Hz, 1 H) 4.47 (dd, $J=10.36$, 3.53 Hz, 1 H) 4.79 - 4.88 (m, 2 H) 5.29 - 5.41 (m, 1 H) 6.12 (d, $J=2.20$ Hz, 1 H) 6.25 (dd, $J=6.06$, 2.32 Hz, 1 H) 7.30 - 7.49 (m, 4 H) 7.71 (d, $J=6.17$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]$ called for $C_{15}H_{14}N_4O$: 267; found 267; RT=2.440 min.

Example 26. Preparation of *N*-((1-aminoisoquinolin-6-yl)methyl)-*N*-methylcyanamide (26)

[0319] To a solution of compound **26.7** (2 g, 8.25 mmol, 1 *eq*) in NMP (20 mL) was added $NH_3 \cdot H_2O$ (18.20 g, 519.26 mmol, 20 mL, 62.94 *eq*). The mixture was stirred at 150 °C for 15 hours. The reaction mixture was quenched by addition H_2O 50 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced



pressure to give a crude product. Compound **26.6** (5 g, crude) was obtained as a yellow oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ called for $\text{C}_9\text{H}_7\text{N}_2\text{Br}$: 224; found 224; $\text{RT}=0.589$ min.

[0320] To a solution of compound **26.6** (2.50 g, 11.21 mmol, 1 *eq*) in THF (40 mL) was added TEA (4.54 g, 44.83 mmol, 6.21 mL, 4 *eq*) and Boc_2O (6.11 g, 28.02 mmol, 6.44 mL, 2.50 *eq*) and DMAP (410.76 mg, 3.36 mmol, 0.30 *eq*). The mixture was stirred at 25°C for 15 hours. The reaction mixture was quenched by addition H_2O 50 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by re-crystallization from ethyl acetate (5 mL) to give compound **26.5** (3 g, 7.09 mmol, 63.22% yield) as yellow solid. ^1H NMR (400 MHz, chloroform-*d*) δ ppm 1.19 - 1.45 (m, 19 H) 7.57 (d, $J=5.77$ Hz, 1 H) 7.71 (dd, $J=8.97, 1.82$ Hz, 1 H) 7.84 (d, $J=8.91$ Hz, 1 H) 8.06 (d, $J=1.76$ Hz, 1 H) 8.46 (d, $J=5.77$ Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ called for $\text{C}_{19}\text{H}_{23}\text{BrN}_2\text{O}_4$: 424; found 424; $\text{RT}=0.896$ min.

[0321] To a solution of compound **26.5** (1.65 g, 3.90 mmol, 1 *eq*) in toluene (120 mL) and MeOH (60 mL) was added TEA (1.58 g, 15.60 mmol, 2.16 mL, 4 *eq*) and $\text{Pd(dppf)Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (318.32 mg, 390 μmol , 0.10 *eq*) under N_2 . The suspension was degassed under vacuum and purged with CO several times. The mixture was stirred under CO (50 psi) at 50°C for 15 hours. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1:1). Compound **26.4** (1.20 g, 2.98 mmol, 76.46% yield) was obtained as a white solid. ^1H NMR (400 MHz, methanol-*d*₄) δ ppm 1.07 - 1.58 (m, 20 H) 4.01 (s, 3 H)

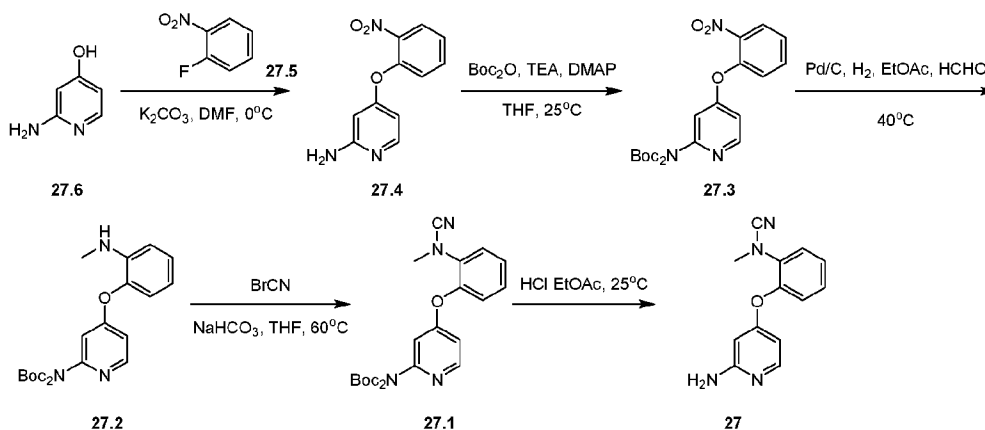
7.99 - 8.04 (m, 1 H) 8.05 - 8.10 (m, 1 H) 8.29 (dd, $J=8.82$, 1.54 Hz, 1 H) 8.47 (d, $J=5.73$ Hz, 1 H) 8.74 (d, $J=1.32$ Hz, 1 H). LCMS (ESI): m/z : [M + H] called for $C_{21}H_{26}N_2O_6$: 403; found 403; RT=1.360 min.

[0322] A mixture of compound **26.4** (100 mg, 248.48 μ mol, 1 *eq*) in HCl/EtOAc (20 mL) was stirred at 25°C for 15 hours. The mixture was filtered and concentrated under reduced pressure to give a residue. Compound **26.3** (50 mg, 209.49 μ mol, 84.31% yield, HCl) was obtained as a yellow solid. LCMS (ESI): m/z : [M + H] called for $C_{11}H_{10}N_2O_2$: 203; found 203; RT=0.119 min. A mixture of compound **26.3** (50 mg, 247.27 μ mol, 1 *eq*) in MeNH₂ (10 mL) was stirred at 80 °C for 15 hours. The mixture was filtered and concentrated under reduced pressure to give compound **26.2** (65 mg, crude) as a brown oil. LCMS (ESI): m/z : [M + H] called for $C_{11}H_{11}N_3O$: 202; found 202; RT=1.093 min.

[0323] To a solution of compound **26.2** (65 mg, 323.01 μ mol, 1 *eq*) in THF (5 mL) was added BH₃-Me₂S (10 M, 323.01 μ L, 10 *eq*) at 0 °C. The mixture was stirred at 70 °C for 4 hours. The reaction mixture was quenched by addition MeOH 20 mL at 25 °C, then concentrated under reduced pressure to give a crude product, to the crude product was added HCl (15 mL), the mixture was stirred at 25 °C for 2 hours and extracted with DCM (25mL x 5). The combined organic layers were washed with saturated brines (5 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (neutral condition). Compound **26.1** (40 mg, 213.63 μ mol, 66.14% yield) was obtained as a yellow oil. LCMS (ESI): m/z : [M + H] called for $C_{11}H_{13}N_3$: 188; found 188; RT=0.506 min.

[0324] To a solution of compound **26.1** (10 mg, 53.41 μ mol, 1 *eq*) in DMF (1 mL) was added DIEA (20.71 mg, 160.23 μ mol, 27.98 μ L, 3 *eq*) and BrCN (5.66 mg, 53.41 μ mol, 3.93 μ L, 1 *eq*). The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition). Product **26** (1 mg, 4.71 μ mol, 8.82% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 2.85 (s, 3 H) 4.33 (s, 2 H) 7.06 (d, $J=5.90$ Hz, 1 H) 7.52 (d, $J=8.41$ Hz, 1 H) 7.65 (s, 1 H) 7.88 (d, $J=8.41$ Hz, 1 H) 7.97 (d, $J=6.02$ Hz, 1 H). LCMS (ESI): m/z : [M + H] called for $C_{12}H_{12}N_4$: 213; found 213; RT=2.098 min.

Example 27. Preparation of *N*-(2-((2-aminopyridin-4-yl)oxy)phenyl)-*N*-methylcyanamide (27)



[0325] To a solution of compound **27.6** (3 g, 27.25 mmol, 1 *eq*) in DMF (100 mL) was added K₂CO₃ (7.53 g, 54.50 mmol, 2 *eq*) and compound **27.5** (4.61 g, 32.70 mmol, 3.44 mL, 1.20 *eq*). The mixture was stirred at 50 °C for 15 hours. The reaction mixture was quenched by addition H₂O 100 mL at 25°C and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1). Compound **27.4** (3.30 g, 14.27 mmol, 52.38% yield) was obtained as a brown solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 6.06 (d, *J*=1.98 Hz, 1 H) 6.32 (dd, *J*=5.84, 2.09 Hz, 1 H) 7.22 - 7.35 (m, 1 H) 7.42 (td, *J*=7.83, 1.10 Hz, 1 H) 7.69 (ddd, *J*=8.21, 7.44, 1.76 Hz, 1 H) 7.99 - 8.16 (m, 2 H). LCMS (ESI): *m/z*: [M + H] called for C₁₁H₉N₃O₃: 232; found 232; RT=0.522 min.

[0326] To a solution of compound **27.4** (3.30 g, 14.27 mmol, 1 *eq*) in THF (50 mL) was added TEA (5.78 g, 57.08 mmol, 7.92 mL, 4 *eq*) and Boc₂O (7.79 g, 35.67 mmol, 8.20 mL, 2.50 *eq*) and DMAP (523.11 mg, 4.28 mmol, 0.30 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O 100 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (10mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **27.3** (3.20 g, 7.42 mmol, 51.98% yield) was obtained as a yellow oil. LCMS (ESI): *m/z*: [M + H] called for C₂₁H₂₅N₃O₇: 432; found 432; RT=0.904 min.

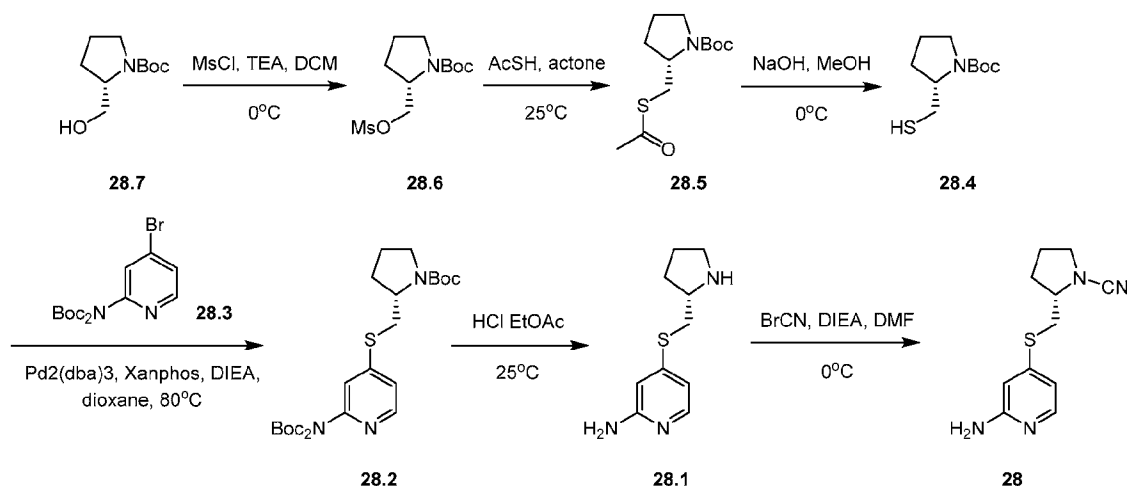
[0327] To a solution of compound **27.3** (1.50 g, 3.48 mmol, 1 *eq*) in MeOH (150 mL) was added Pd-C (10%, 150 mg) and formaldehyde (12 M, 261 μ L, 0.90 *eq*) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (40 psi) at 40 °C for 3 hours. The reaction mixture was filtered and the filter was concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **27.2** (900 mg, 2.17 mmol, 62.25% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₂₂H₂₉N₃O₅: 416; found 416; RT=0.926 min.

[0328] To a solution of compound **27.2** (100 mg, 240.69 μ mol, 1 *eq*) in THF (2 mL) was added BrCN (43.34 mg, 409.17 μ mol, 30.10 μ L, 1.70 *eq*) and NaHCO₃ (60.66 mg, 722.07 μ mol, 28.08 μ L, 3 *eq*). The mixture was stirred at 60 °C for 3 hours. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **27.1** (35 mg, 79.46 μ mol, 33.01% yield) was obtained as a yellow oil. It was combined with a second batch for a total of 55 mg. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.46 (s, 18 H) 3.29 (s, 3 H) 6.75 (dd, *J*=5.71, 2.32 Hz, 1 H) 6.86 (d, *J*=2.26 Hz, 1 H) 7.12 (dd, *J*=7.59, 1.95 Hz, 1 H) 7.30 (td, *J*=5.21, 2.51 Hz, 2 H) 7.37 - 7.41 (m, 1 H) 8.36 (d, *J*=5.65 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₂₃H₂₈N₄O₅: 441; found 441; RT=0.878 min.

[0329] A mixture of compound **27.1** (55 mg, 124.86 μ mol, 1 *eq*) in DCM (1 mL) and TFA (200 μ L) was stirred at 25 °C for 15 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition). Product **27** (2 mg, 8.32 μ mol, 6.67% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.23 - 3.25 (m, 3 H) 5.82 (d, *J*=2.21 Hz, 1 H) 5.97 (s, 2 H) 6.10 (dd, *J*=5.73, 2.43 Hz, 1 H) 7.17 - 7.23 (m, 1 H) 7.28 - 7.37 (m, 2 H) 7.41 - 7.46 (m, 1 H) 7.80 (d, *J*=5.73 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₃H₁₂N₄O: 241; found 241; RT=2.348 min.

Example 28. Preparation of (*S*)-2-(((2-aminopyridin-4-yl)thio)methyl)pyrrolidine-1-carbonitrile (28**)**

[0330] To a mixture of compound **28.7** (1 g, 4.97 mmol, 1 *eq*) and TEA (1.51 g, 14.91 mmol, 2.07 mL, 3 *eq*) in DCM (20 mL) was added methanesulfonyl chloride (683.18 mg, 5.96 mmol, 461.61 μ L, 1.20 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 0.5 hr. The reaction was monitored by TLC (PE:EtOAc=2:1). The aqueous phase was



extracted with DCM (20 mL x 3). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford compound **28.6** (1.80 g, crude) was obtained as a black brown oil. The crude was used for next step
 5 directly. But it didn't work. The crude was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 2:1) to afford pure compound **28.6** (1.67 g, yield 59.87%).

[0331] To a mixture of compound **28.6** (800 mg, 2.86 mmol, 1 *eq*) in acetone (20 mL) was added acetylsulfanylpotassium (327.07 mg, 2.86 mmol, 1 *eq*) at 20°C under N₂. The mixture
 10 was stirred at 50 °C for 15 hours. Filtered and concentrated in vacuum. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 2:1) to afford compound **28.5** (420 mg, 1.62 mmol, 56.62% yield) as a colorless oil. ¹H NMR (400
 15 MHz, methanol-d₄) ppm 1.49 (s, 9H), 1.76 - 2.23 (m, 4H), 2.34 (s, 3H), 2.96 - 3.42 (m, 4H), 3.88 - 3.94 (m, 1 H). LCMS (ESI): m/z: [M + H - 56] calcd for C₁₂H₂₂NO₃S: 204; found 204; RT=0.859 min.

[0332] To a solution of compound **28.5** (200 mg, 771.13 μmol, 1 *eq*) in MeOH (5 mL) was added NaOH (1 M, 925.36 μL, 1.20 *eq*) in one portion at 20°C under N₂. The mixture was
 20 stirred at 20 °C for 3 hours. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **28.4** (100 mg, 460.13 μmol, 59.67% yield) as black brown oil. ¹H NMR (400 MHz, DMSO-d₆) ppm 1.26 - 1.46 (m, 1H), 1.47 (s, 9H), 1.79 - 2 (m, 4H), 2.55 - 2.84 (m, 2H), 3.35 - 3.50 (m, 2 H) 3.82 - 3.88 (m, 1 H).

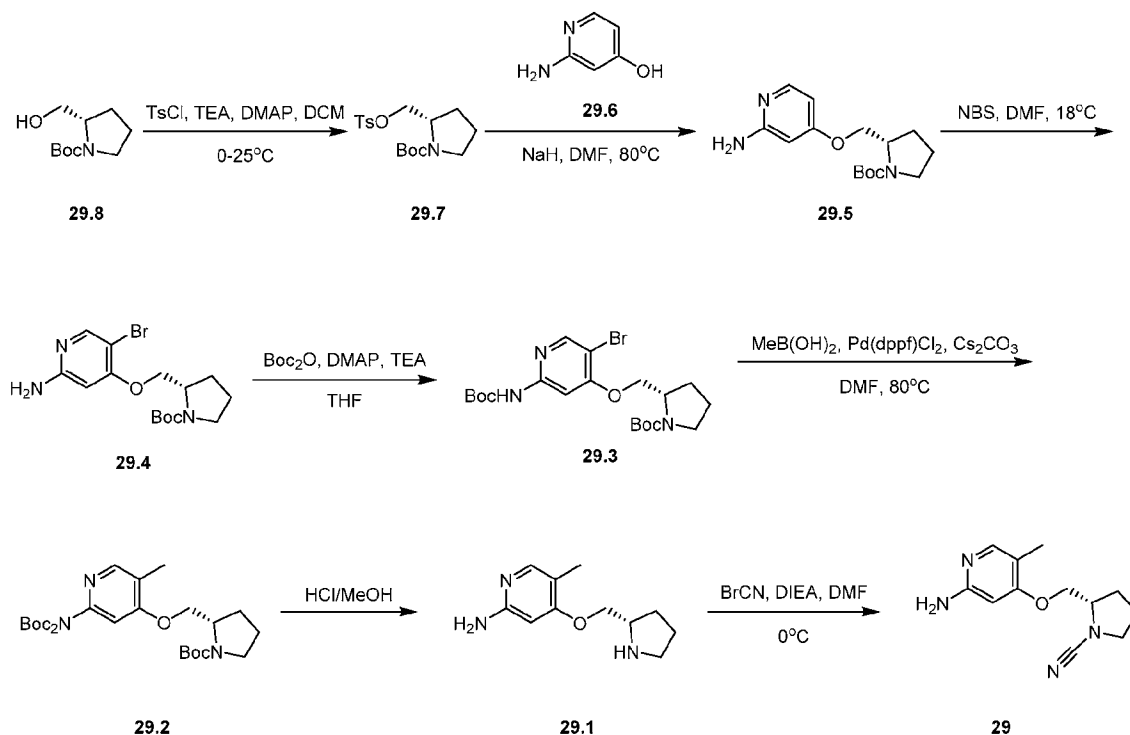
[0333] To a mixture of compound **28.4** (100 mg, 460.13 μ mol, 1 eq) and compound **28.3** (257.61 mg, 690.20 μ mol, 1.50 eq), Xanphos (106.50 mg, 184.05 μ mol, 0.40 eq), DIEA (237.87 mg, 1.84 mmol, 321.45 μ L, 4 eq) in 1,4-dioxane (2 mL) was added Pd₂(dba)₃ (126.41 mg, 138.04 μ mol, 0.30 eq) in one portion at 20°C under N₂. The mixture was stirred at 80 °C for 15 hours. The reaction was monitored by LCMS. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **28.2** (140 mg, crude) was obtained as light yellow oil. ¹H NMR (400 MHz, DMSO-d₆) ppm 1.45 - 1.53 (m, 27H), 1.84 - 2.04 (m, 4H), 2.74 - 2.79 (m, 1H), 3.37 - 3.63 (m, 3H), 4.05 (m, 1 H), 7.15 (s, 1 H), 7.35 (m, 1 H), 8.30 (m, 1H).

[0334] A solution of compound **28.2** (140 mg crude) in HCl/EtOAc (5 mL) was stirred at 20°C for 15 hours under N₂. The reaction was monitored by TLC (SiO₂, PE:EtOAc=1:1). After the reaction was completed, the solution was concentrated in vacuum to give compound **28.1** (50 mg, 156.89 μ mol, 79.96% yield, 3HCl) was obtained as a light yellow solid.

[0335] To a mixture of compound **28.1** (50 mg, 238.88 μ mol, 1 eq) and BrCN (25.30 mg, 238.88 μ mol, 17.57 μ L, 1 eq) in DMF (1 mL) was added DIEA (123.49 mg, 955.52 μ mol, 166.88 μ L, 4 eq) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 10 min. The reaction was monitored by LC-MS promptly until the reaction was completed. The crude was purified by prep-HPLC (basic condition) to afford product **28** (10 mg, 42.68 μ mol, 17.87% yield) as light yellow oil. ¹H NMR (400 MHz, DMSO-d₆) ppm 1.79 - 1.94 (m, 1 H), 1.94 - 1.98 (m, 2 H), 2.11 - 2.15 (m, 1 H), 2.88 - 2.94 (m, 1 H), 3.35 - 3.54 (m, 3 H), 3.84 - 3.85 (m, 1 H), 4.48 (s, 2 H), 6.40 (s, 1 H), 6.54 (dd, *J*=1.6 Hz, *J*=5.6 Hz, 1 H), 7.91 (d, *J*=5.6 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₄N₄S: 235; found 235; RT=2.209 min.

Example 29. Preparation of (S)-2-(((2-amino-5-methylpyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (29)

[0336] To a mixture of compound **29.8** (5 g, 24.84 mmol, 1 eq) and 4-methylbenzenesulfonyl chloride (5.68 g, 29.81 mmol, 1.20 eq) in DCM (50 mL) was added TEA (3.77 g, 37.26 mmol, 5.16 mL, 1.50 eq) and DMAP (485.62 mg, 3.97 mmol, 0.16 eq) in one portion at 0°C under N₂. The mixture was then heated to 25 °C and stirred for 10 hours. The reaction mixture was diluted with H₂O 50 mL and extracted with DCM 30 mL (30 mL x



3). The combined organic layers were washed with brine 60 mL (60 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **29.7** (8.90 g, crude) as a yellow oil. LCMS (ESI): m/z: [M + H] calcd for C₁₇H₂₅NO₅S: 355; found 300,256; RT=0.890 min.

[0337] To a mixture of compound **29.7** (8.84 g, 24.87 mmol, 1 eq) and compound **29.6** (3.01 g, 27.36 mmol, 1.10 eq) in DMF (100 mL) was added NaH (895.44 mg, 37.31 mmol, 1.50 eq) portionwise at 80°C under N₂. The mixture was stirred at 80°C for 10 hours. The reaction mixture was quenched by addition H₂O 100 mL, and then extracted with EtOAc 80 mL (80 mL x 3). The combined organic layers were washed with brine 150 mL (150 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **29.5** (4.50 g, 15.34 mmol, 61.68% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.40 (s, 9 H) 1.71 - 1.95 (m, 4 H) 3.28 (br s, 2 H) 3.63 - 3.91 (m, 1 H) 3.97 - 4.15 (m, 1 H) 4.05 (br dd, *J*=14.18, 7.03 Hz, 1 H) 5.85 - 6.05 (m, 1 H) 6.22 (br d, *J*=4.39 Hz, 1 H) 7.81 (br d, *J*=5.14 Hz, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₂: 293; found 294; RT=0.692 min.

[0338] To a mixture of compound **29.5** (1 g, 3.41 mmol, 1 eq) in DMF (15 mL) was added NBS (606.69 mg, 3.41 mmol, 1 eq) in one portion at 18°C under N₂. The mixture was stirred at 18 °C for 3 hours. The reaction mixture was quenched by addition H₂O 15 mL and

extracted with EtOAc 10 mL (10 mL x 3). The combined organic layers were washed with brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **29.4** (1 g, 2.69 mmol, 78.78% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.38 (br d, *J*=4.19 Hz, 9 H) 1.72 - 1.83 (m, 1 H) 1.93 (br s, 1 H) 1.98 - 2.17 (m, 2 H) 3.24 - 3.31 (m, 2 H) 3.94 - 4.10 (m, 4 H) 6.02 (s, 2 H) 6.10 (s, 1 H) 7.72 - 7.92 (m, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₅H₂₂N₃BrO₃: 372; found 372, 374; RT=0.763 min.

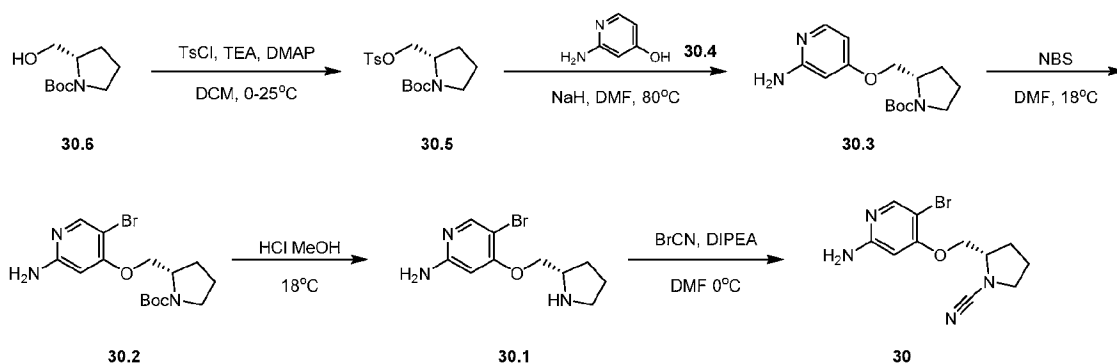
[0339] To a mixture of compound **29.4** (800 mg, 2.15 mmol, 1 *eq*) and DMAP (42.01 mg, 344 μmol, 0.16 *eq*), TEA (869.84 mg, 8.60 mmol, 1.19 mL, 4 *eq*) in THF (15 mL) was added Boc₂O (1.17 g, 5.38 mmol, 1.23 mL, 2.50 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 30 mL (10 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **29.3** (900 mg, 1.57 mmol, 73.02% yield) as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.40 (s, 27 H) 1.81 (br s, 1 H) 1.95 - 2.17 (m, 3 H) 3.28 - 3.48 (m, 2 H) 4.13 (br s, 3 H) 6.70 - 6.95 (m, 1 H) 8.33 (br s, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₂₅H₃₈N₃BrO₇: 572; found 574, 572; RT=18 min.

[0340] To a mixture of compound **29.3** (750 mg, 1.59 mmol, 1 *eq*), Cs₂CO₃ (2.07 g, 6.36 mmol, 4 *eq*) and methylboronic acid (142.77 mg, 2.38 mmol, 1.50 *eq*) in DMF (15 mL) was added Pd(dppf)Cl₂ (349.03 mg, 477 μmol, 0.30 *eq*) in one portion at 80 °C under N₂. The mixture was stirred at 80 °C for 10 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EA 30 mL (10 mL x 3). The combined organic layers were washed with brine 30 mL (30 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **29.2** (800 mg, crude) as a yellow solid. LCMS (ESI): *m/z*: [M + H] calcd for C₂₁H₃₃N₃O₅: 407; found 208; RT=0.150 min.

[0341] Compound **29.2** (800 mg, 1.58 mmol, 1 *eq*) was added into a solution of HCl/MeOH (15 mL). The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition) to give compound **29.1** (200 mg, 964.92 μmol, 61.07% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₇N₃O: 207; found 208; RT=0.173 min.

[0342] To a mixture of compound **29.1** (100 mg, 482.46 μmol , 1 *eq*) and DIPEA (249.41 mg, 1.93 mmol, 337.05 μL , 4 *eq*) in DMF (3 mL) was added CNBr (56.21 mg, 530.71 μmol , 39.04 μL , 1.10 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition) to give product **29** (10 mg, 43.05 μmol , 8.92% yield) as a yellow solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.87 - 2.04 (m, 4 H) 2.07 (s, 2 H) 2.10 - 2.21 (m, 1 H) 3.41 - 3.65 (m, 2 H) 3.91 - 4.12 (m, 2 H) 5.95 (s, 1 H) 7.72 (s, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₂H₁₆N₄O: 232; found 233; RT=2.181 min.

Example 30. Preparation of (*S*)-2-(((2-amino-5-bromopyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (**30**)



[0343] To a mixture of compound **30.6** (5 g, 24.84 mmol, 1 *eq*) and 4-methylbenzenesulfonyl chloride (5.68 g, 29.81 mmol, 1.20 *eq*) in DCM (50 mL) was added TEA (3.77 g, 37.26 mmol, 5.16 mL, 1.50 *eq*) and DMAP (485.62 mg, 3.97 mmol, 0.16 *eq*) in one portion at 0°C under N₂. The mixture was then heated to 25°C and stirred for 10 hours. The reaction mixture was diluted with H₂O 50 mL and extracted with DCM 90 mL (30 mL x 3). The combined organic layers were washed with brine 60 mL (60 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **30.5** (8.90 g, crude) as a yellow oil. LCMS (ESI): *m/z*: [M + H] calcd for C₁₇H₂₅NO₅S: 356; found 300; RT=0.890 min.

[0344] To a mixture of compound **30.5** (8.84 g, 24.87 mmol, 1 *eq*) and compound **30.4** (3.01 g, 27.36 mmol, 1.10 *eq*) in DMF (100 mL) was added NaH (895.44 mg, 37.31 mmol, 1.50 *eq*) portionwise at 80°C under N₂. The mixture was stirred at 80°C for 10 hours. The reaction mixture was quenched by addition H₂O 1000 mL, and then extracted with EtOAc 240 mL (80 mL x 3). The combined organic layers were washed with brine 150 mL (150 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue.

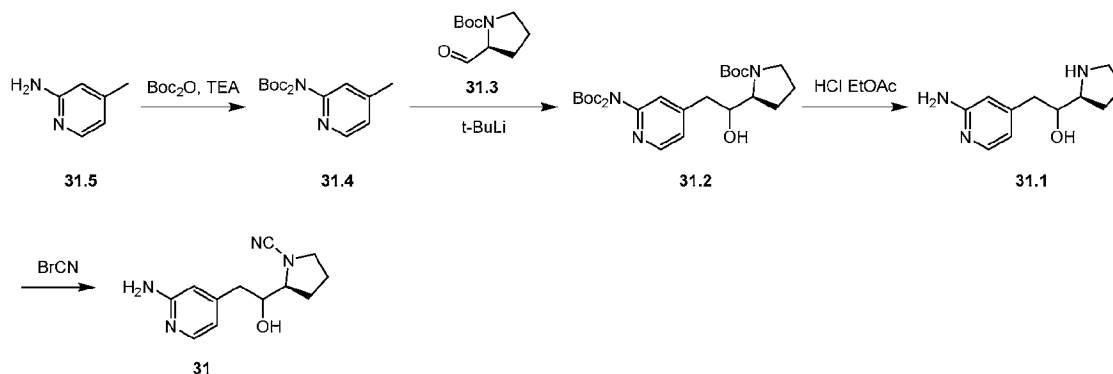
The residue was purified by column chromatography (SiO₂, DCM/MeOH=10:1) to give compound **30.3** (4.50 g, 15.34 mmol, 61.68% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 294; found 294; RT=0.692 min.

[0345] To a mixture of compound **30.3** (1 g, 3.41 mmol, 1 *eq*) in DMF (15 mL) was added NBS (606.69 mg, 3.41 mmol, 1 *eq*) in one portion at 18°C under N₂. The mixture was stirred at 18°C for 3 hours. The reaction mixture was quenched by addition H₂O 15 mL and extracted with EtOAc 30 mL (10 mL x 3). The combined organic layers were washed with brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **30.2** (1 g, 2.69 mmol, 78.78% yield) as a colorless oil. LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₂BrN₃O₃: 372; found 372, 374; RT=0.763 min.

[0346] Compound **30.2** (100 mg, 268.63 μmol, 1 *eq*) was added into a solution of HCl/MeOH (5 mL). The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **30.1** (120 mg, 440.95 μmol, 164.15% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₄N₃OBr: 272; found 272,274; RT=0.096 min.

[0347] To a mixture of compound **30.1** (100 mg, 367.46 μmol, 1 *eq*) and DIPEA (189.96 mg, 1.47 mmol, 256.70 μL, 4 *eq*) in DMF (3 mL) was added CNBr (42.81 mg, 404.20 μmol, 29.73 μL, 1.10 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (TFA condition) to give product **30** (20 mg, 67.31 μmol, 18.32% yield) as a yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₃N₄O: 297; found 297,299; RT=2.364 min.

Example 31. Preparation of (2*S*)-2-(2-(2-aminopyridin-4-yl)-1-hydroxyethyl)pyrrolidine-1-carbonitrile (31**)**



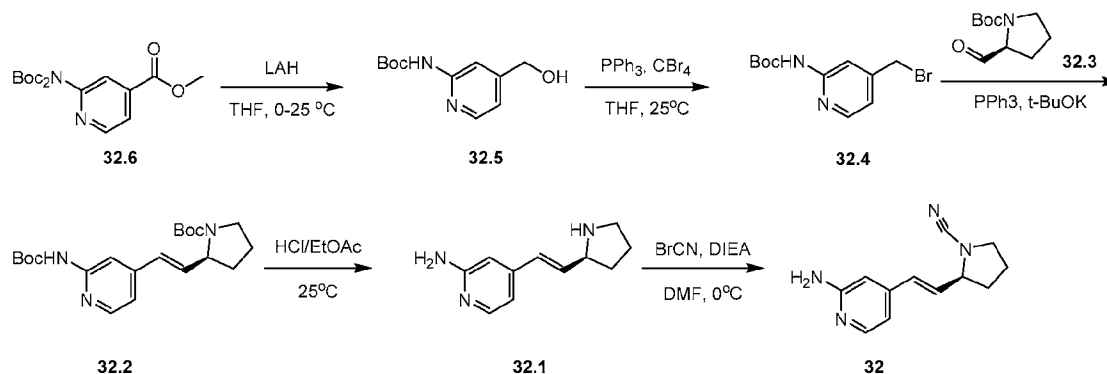
[0348] To a solution of compound **31.5** (1 g, 9.25 mmol, 1 *eq*) in THF (50 mL) was added Boc₂O (6.06 g, 27.75 mmol, 6.38 mL, 3 *eq*), TEA (3.74 g, 37 mmol, 5.13 mL, 4 *eq*) and DMAP (339.02 mg, 2.77 mmol, 0.30 *eq*) at 25°C under N₂. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water (30 mL), extracted with EtOAc (50 mL x 3). The organic phase was separated, washed with saturated NaCl (20 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound **31.4** (1.50 g, 4.86 mmol, 52.59% yield) was obtained as a yellow solid.

[0349] To a solution of compound **31.4** (1.50 g, 4.86 mmol, 1 *eq*) in THF (20 mL) was added t-BuLi (1.3 M, 7.48 mL, 2 *eq*) drop-wise at -78°C under N₂. During which the temperature was maintained below -78°C. The reaction mixture was stirred at -78°C for 1 h. Then compound **31.3** (969.21 mg, 4.86 mmol, 1 *eq*) was added to above mixture. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water (10 mL), extracted with EtOAc (20 mL x 3). The organic phase was separated, washed with saturated NaCl (10 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound **31.2** (500 mg, 984.99 μmol, 20.27% yield) was obtained as a yellow oil.

[0350] To a solution of compound **31.2** (500 mg, 984.99 μmol, 1 *eq*) in HCl/EtOAc (10 mL) was stirred at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue. Compound **31.1** (400 mg, crude) was obtained as a yellow oil.

[0351] To a solution of compound **31.1** (400 mg, 1.43 mmol, 1 *eq*, 2HCl) in DMF (5 mL) was added DIEA (553.51 mg, 4.28 mmol, 747.99 μL, 3 *eq*) and BrCN (151.21 mg, 1.43 mmol, 105.01 μL, 1 *eq*) at 25°C under N₂. The resulting mixture was stirred at 25°C for 2 hours. The reaction mixture was added water (10 mL), extracted with EtOAc (10 mL x 3). The organic phase was separated, washed with saturated NaCl (10 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition). Product **30** (15 mg, 64.58 μmol, 4.52% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₂H₁₆N₄O₂:232; found 233; RT=2.141, 2.394 min. ¹H NMR (400 MHz, methanol-d₄) δ ppm 1.70 - 2.12 (m, 4 H) 2.58 - 2.60 (m, 1 H) 2.91 - 2.98 (m, 1 H) 3.46 - 3.99 (m, 2 H) 4.13 - 4.16 (m, 1 H) 5.12 - 5.14 (m, 1 H) 6.48 - 6.58 (m, 2 H) 7.78 - 7.82 (m, 1 H)

Example 32. Preparation of (*S,E*)-2-(2-(2-aminopyridin-4-yl)vinyl)pyrrolidine-1-carbonitrile (32**)**



[0352] To a solution of compound **32.6** (5 g, 14.19 mmol, 1 *eq*) in THF (50 mL) was added LAH (1.35 g, 35.48 mmol, 2.50 *eq*) at 0°C and stirred for 1 hour. The mixture was warmed to 25°C gradually and stirred for 11 hr. The reaction mixture was quenched by addition 8% NaOH solution 2 mL at 25°C, and then diluted with H₂O 20 mL and extracted with EtOAc 60 mL (20 mL x 3). The combined organic layers were washed with brines 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **32.5** (1.50 g, 6.69 mmol, 47.14% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₆N₂O₃: 224; found 225; RT=0.404 min.

[0353] To a solution of compound **32.5** (1.50 g, 6.69 mmol, 1 *eq*) in THF (15 mL) was added CBr₄ (3.33 g, 10.03 mmol, 1.50 *eq*) and PPh₃ (2.63 g, 10.03 mmol, 1.50 *eq*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was diluted with H₂O 20 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 20 mL (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate= 3:1) to give compound **32.4** (1.10 g, 3.83 mmol, 57.26% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.54 (s, 9 H) 4.36 (s, 2 H) 6.97 (dd, *J*=5.29, 1.54 Hz, 1 H) 7.94 - 8.08 (m, 1 H) 8.29 (d, *J*=5.29 Hz, 1 H) 9.23 (s, 1 H)

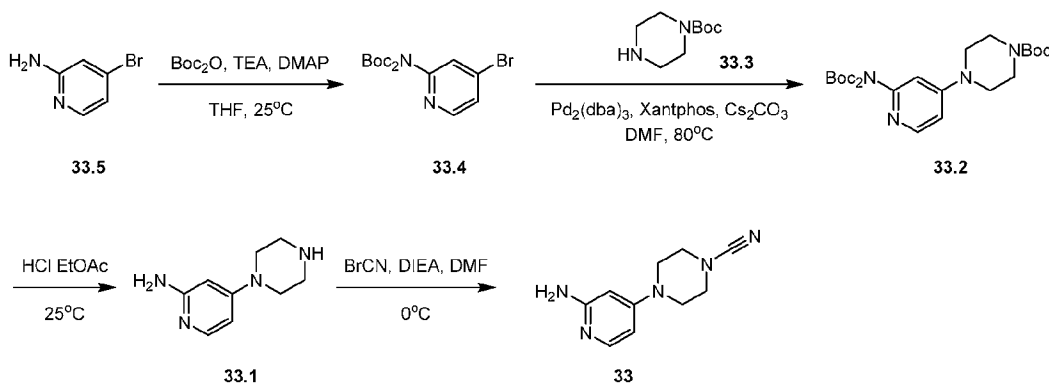
[0354] To a solution of compound **32.4** (400 mg, 1.39 mmol, 1 *eq*) in toluene (7 mL) was added PPh₃ (401.04 mg, 1.53 mmol, 1.10 *eq*) under nitrogen and reflux 120°C for 3 hours. After cooling to 25°C, the white solid was filtered off, washed with EtOAc and dried under vacuum. Then the mixture was stirred in THF (4 mL) under nitrogen and t-BuOK (171.57 mg, 1.53 mmol, 1.10 *eq*) was added. The mixture was stirred at 70°C for 1 hr. After cooling

to 25°C, compound **32.3** (415.44 mg, 2.09 mmol, 1.50 *eq*) in THF (1 mL) was added to the reaction flask and reflux for 30 min. The reaction mixture was diluted with H₂O 15 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 15 mL (15 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **32.2** (200 mg, 513.49 μmol, 36.94% yield) as a brown oil. LCMS (ESI): *m/z*: [M + H] calcd for C₂₁H₃₁N₃O₄: 389; found 390; RT=1.508 min.

[0355] To a solution of compound **32.2** (180 mg, 462.14 μmol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 12 hours. The reaction mixture was concentrated under reduced pressure to remove solvent to give compound **32.1** (150 mg, crude) as a brown oil. LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₅N₃:189; found 190; RT=0.382 min.

[0356] To a solution of compound **32.1** (150 mg, 792.56 μmol, 1 *eq*) in DMF (2 mL) was added DIEA (409.72 mg, 3.17 mmol, 553.68 μL, 4 *eq*) at 0°C. When the pH >9, the mixture was added BrCN (83.95 mg, 792.56 μmol, 58.30 μL, 1 *eq*) and stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (column: YMC-Actus Triart C18 150x30 5u; mobile phase: [water (10mM NH₄HCO₃)-ACN];B%: 10%-30%,12 min) to give product **32** (5 mg, 23.34 μmol, 2.94% yield) as a brown oil. LCMS (ESI): *m/z*: [M + H] calcd for C₁₂H₁₄N₄:214; found 215; RT=2.160 min. ¹H NMR (400 MHz, methanol-d₄) δ ppm 1.63 - 1.74 (m, 1 H) 1.78 - 2 (m, 3 H) 2.03 - 2.15 (m, 1 H) 3.33 - 3.54 (m, 2 H) 4.16 (q, J=7.01 Hz, 1 H) 6.22 - 6.30 (m, 1 H) 6.42 (s, 1 H) 6.45 - 6.49 (m, 1 H) 6.62 (d, J=4.52 Hz, 1 H) 7.65 - 7.82 (m, 1 H).

Example 33. Preparation of 4-(2-aminopyridin-4-yl)piperazine-1-carbonitrile (**33**)



[0357] To a solution of compound **33.5** (1 g, 5.78 mmol, 1 *eq*) in THF (20 mL) was added Boc₂O (3.15 g, 14.45 mmol, 3.32 mL, 2.50 *eq*), TEA (2.34 g, 23.12 mmol, 3.21 mL, 4 *eq*) and DMAP (211.84 mg, 1.73 mmol, 0.30 *eq*) at 25°C under N₂. The result mixture was

stirred at 25°C for 16 hours. The reaction mixture was added water (20 mL), extracted with EtOAc (20 mL x 3). The organic phase was separated, washed with saturated NaCl (10 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 1:1). Compound **33.4** (1 g, 2.68 mmol, 46.35% yield) was obtained as a yellow solid.

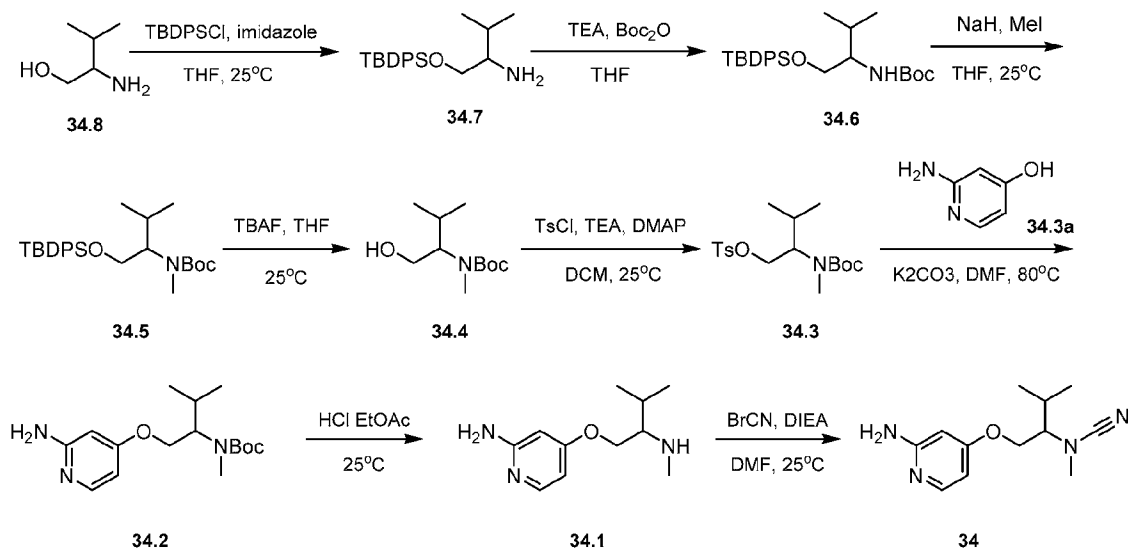
[0358] To a solution of compound **33.4** (1 g, 2.68 mmol, 1 *eq*) in DMF (10 mL) was added compound **33.3** (499.01 mg, 2.68 mmol, 1 *eq*) Pd₂(dba)₃ (245.34 mg, 267.92 μmol, 0.10 *eq*) and Cs₂CO₃ (2.62 g, 8.04 mmol, 3 *eq*) at 25°C under N₂. The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was added water (10 mL), extracted with EtOAc (10 mL x 3). The organic phase was separated, washed with saturated NaCl (10 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Compound **33.2** (500 mg, 1.04 mmol, 38.98% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] called for C₂₄H₃₈N₄O₆: 479; found 479; RT=0.771 min.

[0359] To a solution of compound **33.2** (500 mg, 1.04 mmol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25°C for 16 hours. The reaction mixture was concentrated under reduced pressure to give a residue. Compound **33.1** (100 mg, 561.07 μmol, 53.95% yield) was obtained as a white solid.

[0360] To a solution of compound **33.1** (100 mg, 398.15 μmol, 1 *eq*, 2HCl) in DMF (3 mL) was added DIEA (205.83 mg, 1.59 mmol, 278.15 μL, 4 *eq*) and BrCN (42.17 mg, 398.15 μmol, 29.28 μL, 1 *eq*). The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition). Product **33** (2 mg, 9.84 μmol, 2.47% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 3.33 - 3.38 (m, 4 H) 3.40 - 3.46 (m, 4 H) 6 (s, 1 H) 6.22 - 6.32 (m, 1 H) 7.62 (d, *J*=6.39 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₀H₁₃N₅: 204; found 204; RT=1.133 min.

Example 34. Preparation of N-(1-((2-aminopyridin-4-yl)oxy)-3-methylbutan-2-yl)-N-methylcyanamide (**34**)

[0361] To a solution of compound **34.8** (1 g, 9.69 mmol, 1.06 mL, 1 *eq*) in THF (15 mL) was added IMIDAZOLE (2.64 g, 38.76 mmol, 4 *eq*) and TBDPSCl (5.33 g, 19.38 mmol, 4.98 mL, 2 *eq*). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C, and extracted with EtOAc (50 mL x 3). The combined



organic layers were washed with saturated brine (25 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. Compound **34.7** (4 g, crude) was obtained as a yellow oil, and the crude product was used into the next step

5 without further purification.

[0362] To a solution of compound **34.7** (4 g, 11.71 mmol, 1 eq) in THF (30 mL) was added TEA (4.74 g, 46.84 mmol, 6.49 mL, 4 eq) and Boc₂O (3.83 g, 17.57 mmol, 4.04 mL, 1.50 eq). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C, and extracted with ethyl acetate (50 mL x 3). The combined

10 organic layers were washed with saturated brine (25 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1). Compound **34.6** (3 g, 6.79 mmol, 93.69% yield) was obtained as a colorless oil.

[0363] To a solution of compound **34.6** (1 g, 2.26 mmol, 1 eq) in THF (20 mL) was added

15 NaH (108.48 mg, 4.52 mmol, 2 eq) the mixture was stirred at 25°C for 1 hr. Then to the mixture was added MeI (384.94 mg, 2.71 mmol, 168.83 µL, 1.20 eq). The mixture was stirred at 0 °C for 12 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and

20 concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **34.5** (600 mg, 1.32 mmol, 58.41% yield) was obtained as a yellow oil.

[0364] To a solution of compound **34.5** (600 mg, 1.32 mmol, 1 *eq*) in THF (15 mL) was added TBAF (345.13 mg, 1.32 mmol, 1 *eq*) the mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 2:1). Compound **34.4** (250 mg, 1.15 mmol, 87.16% yield) was obtained as a yellow oil.

[0365] To a solution of compound **34.4** (250 mg, 1.15 mmol, 1 *eq*) in DCM (5 mL) was added TEA (349.11 mg, 3.45 mmol, 478.23 µL, 3 *eq*) and DMAP (28.10 mg, 230 µmol, 0.20 *eq*) and TosCl (263.10 mg, 1.38 mmol, 1.20 *eq*). The mixture was stirred at 25 °C for 2 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **34.3** (500 mg, crude) was obtained as a yellow oil.

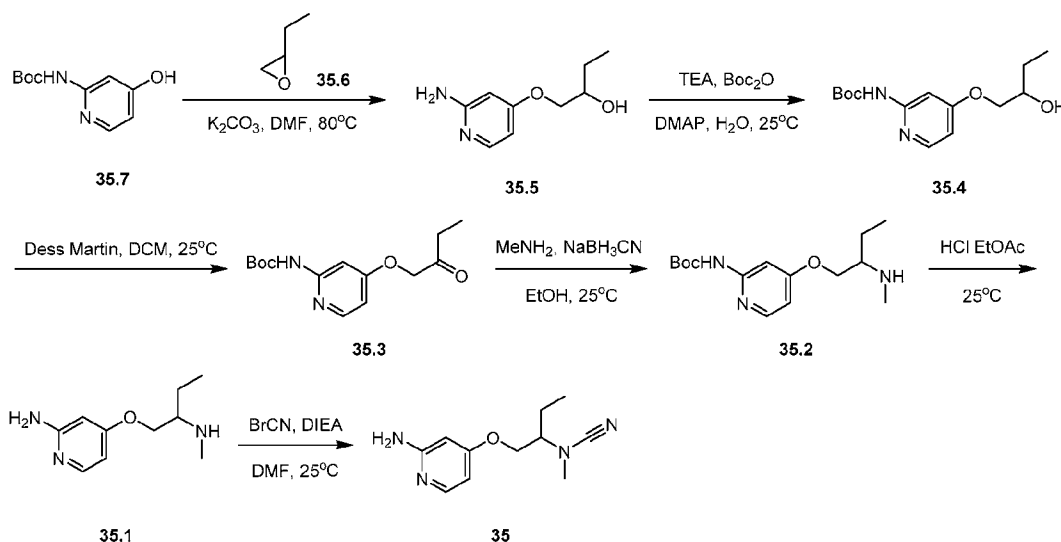
[0366] To a solution of compound **34.3** (400 mg, 1.08 mmol, 1 *eq*) and compound **34.3a** (118.56 mg, 1.08 mmol, 1 *eq*) in DMF (10 mL) was added K₂CO₃ (595.27 mg, 4.31 mmol, 4 *eq*). The mixture was stirred at 80 °C for 13 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 10:1). Compound **34.2** (200 mg, 646.41 µmol, 60.03% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₁₆H₂₇N₃O₃: 310; found 310; RT=0.591 min.

[0367] A mixture of compound **34.2** (200 mg, 646.41 µmol, 1 *eq*) in HCl/EtOAc (15 mL) was stirred at 25 °C for 13 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **34.1** (170 mg, 602.39 µmol, 93.19% yield, 2HCl) was obtained as a yellow solid. LCMS (ESI): m/z: [M + H] called for C₁₁H₁₉N₃O: 210; found 210; RT=0.098 min.

[0368] To a solution of compound **34.1** (170 mg, 602.39 µmol, 1 *eq*, 2HCl) in DMF (2 mL) was added DIEA (311.41 mg, 2.41 mmol, 420.83 µL, 4 *eq*) and BrCN (63.80 mg, 602.39 µmol, 44.31 µL, 1 *eq*). The mixture was stirred at 0 °C for 10 min. The residue was purified

by prep-HPLC (neutral condition). Product **34** (40 mg, 170.72 μ mol, 28.34% yield) was obtained as a yellow oil. ^1H NMR (400 MHz, methanol- d_4) δ ppm 0.96 - 1.17 (m, 6 H) 1.87 - 2.19 (m, 1 H) 2.88 - 3.07 (m, 4 H) 4.02 - 4.35 (m, 2 H) 6.14 (d, $J=1.76$ Hz, 1 H) 6.30 (dd, $J=6.06$, 1.87 Hz, 1 H) 7.73 (d, $J=5.95$ Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ called for $\text{C}_{12}\text{H}_{18}\text{N}_4\text{O}$: 235; found 235; RT=2.295 min.

Example 35. Preparation of N-(1-((2-aminopyridin-4-yl)oxy)butan-2-yl)-N-methylcyanamide (35)



[0369] To a solution of compound **35.7** (1 g, 4.76 mmol, 1 *eq*) and compound **35.6** (342.98 mg, 4.76 mmol, 413.23 μL , 1 *eq*) in DMF (25 mL) was added K_2CO_3 (1.97 g, 14.27 mmol, 3 *eq*). The mixture was stirred at 80°C for 14 hours. The reaction mixture was quenched by addition H_2O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **35.5** (2.5 g, crude) was obtained as a yellow oil. It was used into the next step without further purification.

[0370] To a solution of compound **35.5** (2 g, 3.29 mmol, 1 *eq*) in THF (20 mL) and H_2O (30 mL) was added TEA (1.67 g, 16.46 mmol, 2.28 mL, 5 *eq*) and Boc_2O (2.16 g, 9.88 mmol, 2.27 mL, 3 *eq*) and DMAP (120.68 mg, 987.82 μmol , 0.30 *eq*). The mixture was stirred at 25°C for 15 hours. The reaction mixture was quenched by addition H_2O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column

chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1). Compound **35.4** (230 mg, 814.65 μ mol, 24.74% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₁₄H₂₂N₄O₂: 283; found 283; RT=0.654 min.

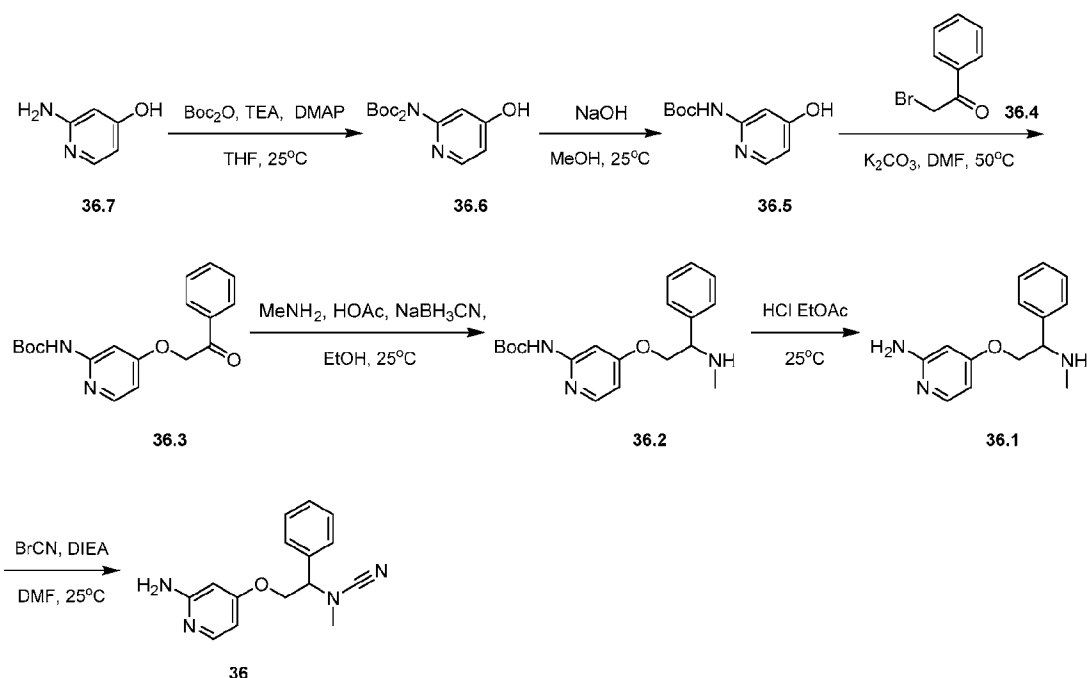
[0371] To a solution of compound **35.4** (230 mg, 814.65 μ mol, 1 *eq*) in DCM (5 mL) was added Dess-Martin periodinane (691.05 mg, 1.63 mmol, 504.42 μ L, 2 *eq*) mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 2:1). Compound **35.3** (225 mg, 802.65 μ mol, 98.53% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.13 (t, *J*=7.28 Hz, 3 H) 1.48 - 1.59 (m, 1 H) 1.48 - 1.59 (m, 10 H) 2.63 (q, *J*=7.28 Hz, 2 H) 4.65 (s, 2 H) 6.53 (dd, *J*=5.73, 2.43 Hz, 1 H) 7.58 (d, *J*=1.98 Hz, 1 H) 8.07 - 8.22 (m, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₄H₂₀N₄O₂: 281; found 281; RT=0.615 min.

[0372] A mixture of compound **35.3** (100 mg, 356.74 μ mol, 1 *eq*) in MeNH₂ (2 mL) was stirred at 0 °C for 1 hr. To the mixture was added HOAc (32.13 mg, 535.10 μ mol, 30.60 μ L, 1.50 *eq*) make the mixture to pH = 4 and then added NaBH₃CN (89.67 mg, 1.43 mmol, 4 *eq*). The mixture was stirred at 25°C for 12 hours. The reaction mixture was quenched by addition saturated NaHCO₃ 20 mL at 25°C make the pH>7 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 10:1). Compound **35.2** (80 mg, 270.84 μ mol, 75.92% yield) was obtained as a yellow oil. It was combined with a second batch for a total of 160 mg. LCMS (ESI): m/z: [M + H] called for C₁₅H₂₅N₃O₃: 296; found 296; RT=0.520 min.

[0373] A mixture of compound **35.2** (160 mg, 541.68 μ mol, 1 *eq*) in HCl/EtOAc (5 mL) was stirred at 25 °C for 13 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **35.1** (140 mg, 522.04 μ mol, 96.38% yield, 2HCl) was obtained as a yellow oil.

[0374] To a solution of compound **35.1** (140 mg, 522.04 μmol , 1 *eq*, 2HCl) in DMF (2 mL) was added DIEA (269.87 mg, 2.09 mmol, 364.69 μL , 4 *eq*) and BrCN (55.29 mg, 522.04 μmol , 38.40 μL , 1 *eq*). The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition). Product **35** (40 mg, 181.60 μmol , 34.79% yield) was obtained as a yellow oil. ^1H NMR (400 MHz, methanol-*d*₄) δ ppm 1.07 (t, *J*=7.39 Hz, 3 H) 1.60 - 1.82 (m, 2 H) 2.98 (s, 3 H) 3.15 - 3.30 (m, 1 H) 3.97 - 4.19 (m, 2 H) 6.13 (d, *J*=2.21 Hz, 1 H) 6.28 (dd, *J*=6.17, 2.20 Hz, 1 H) 7.73 (d, *J*=6.17 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₆N₄O: 221; found 221; RT=2.115 min.

Example 36. Preparation of *N*-(2-((2-aminopyridin-4-yl)oxy)-1-phenylethyl)-*N*-methylcyanamide (**36**)



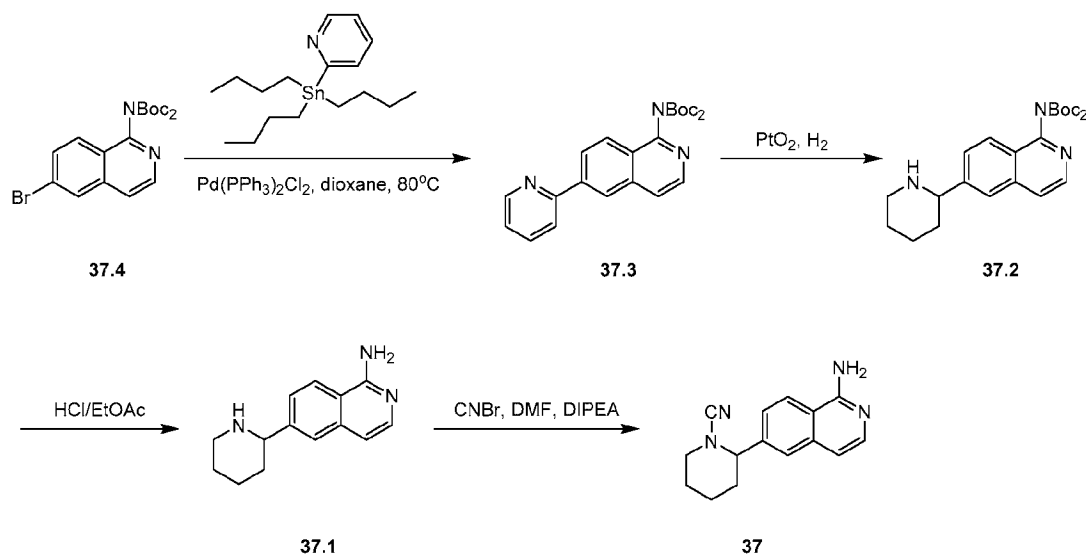
[0375] The solution of **36.7** (5 g, 45.41 mmol, 1 *eq*) in THF (50 mL) was added triethyl amine (18.38 g, 181.64 mmol, 25.18 mL, 4 *eq*) and Boc₂O (29.73 g, 136.23 mmol, 31.29 mL, 3 *eq*) and DMAP (1.66 g, 13.62 mmol, 0.30 *eq*). The mixture was stirred at 25 °C for 16 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25 °C, and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brine (25 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The crude product compound **36.6** (4 g, 9.75 mmol,) was used into the next step without further purification. LCMS (ESI): *m/z*: [M + H] calcd for C₂₀H₃₀N₂O₇: 311; found 411; RT= 0.941 min.

- [0376] To a solution of compound **36.6** (3 g, 9.67 mmol, 1 *eq*) in MeOH (40 mL) and H₂O (4 mL) was added NaOH (966.65 mg, 24.17 mmol, 2.50 *eq*). The mixture was stirred at 25 °C for 16 hours. The rethyl acetate mixture was quenched by addition H₂O 25 mL at 25 °C, and extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with saturated brine (25 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=4/1) to give a compound **36.5** (1.50 g, 7.14 mmol, 73.79% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₀H₁₄O₃N₂: 211; found 211; RT= 0.352 min.
- 10 [0377] To a solution of compound **36.5** (500 mg, 2.38 mmol, 1 *eq*) in DMF (30 mL) was added K₂CO₃ (986.82 mg, 7.14 mmol, 3 *eq*) and compound 36.4 (570 mg, 2.86 mmol, 1.2 *eq*). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25 °C, and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brine (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a compound **36.3** (260 mg, 791.81 μmol, crude) as a white solid, and the crude product was without further purification. LCMS (ESI): *m/z*: [M + H] calcd for C₁₈H₂₀O₄N₂: 329; found 329; RT= 0.701 min.
- 15 [0378] To a solution of compound **36.3** (200 mg, 609.09 μmol, 1 *eq*) in NH₂CH₃ (2 mL) was added HOAc (54.86 mg, 913.63 μmol, 52.25 μL, 1.50 *eq*) and NaBH₃CN (153.10 mg, 2.44 mmol, 4 *eq*). The mixture was stirred at 25 °C for 14 hours. The rethyl acetate mixture was quenched by addition H₂O 50 mL at 25 °C, and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brine (25 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2/1) to give a compound **36.2** (80 mg, 232.95 μmol, 38.25% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.50 (s, 9 H) 2.35 (s, 3 H) 3.95 - 4.06 (m, 2 H) 4.07 - 4.14 (m, 1 H) 6.49 (dd, *J*=5.70, 2.19 Hz, 1 H) 7.28 - 7.33 (m, 1 H) 7.34 - 7.44 (m, 4 H) 7.50 (d, *J*=1.75 Hz, 1 H) 8.03 (d, *J*=5.70 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₉H₂₅O₃N₃: 343; found 343; RT= 0.587 min.
- 25 [0379] To a solution of compound **36.2** (80 mg, 232.95 μmol, 1 *eq*) in HCl/EtOAc (15 mL). The mixture was stirred at 25 °C for 14 hours. The rethyl acetate mixture was filtered and concentrated under to give the compound **36.1** (50 mg, 205.51 μmol, 88.22% yield) as a
- 30

white solid. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{14}H_{17}N_3O$: 244; found 244; RT = 0.104 min.

[0380] To a solution of compound **36.1** (50 mg, 308.26 μ mol, 1 *eq*) in DMF (5 mL) was added BrCN (32.65 mg, 308.26 μ mol, 22.67 μ L, 1 *eq*) and DIETHYL ACETATE (159.36 mg, 1.23 mmol, 215.35 μ L, 4 *eq*). The mixture was stirred at 0 °C for 0.5 hour. The residue was purified by prep-HPLC (neutral condition) to give product **36** (25 mg, 93.18 μ mol, 45.34% yield) as a white solid. 1H NMR (400 MHz, chloroform-*d*) δ ppm 1.57 (s, 9 H) 2.87 (s, 3 H) 4.14 - 4.33 (m, 2 H) 4.33 - 4.55 (m, 3 H) 5.99 (d, J =1.98 Hz, 2 H) 6.27 (dd, J =5.95, 2.20 Hz, 1 H) 7.36 - 7.53 (m, 5 H) 7.90 (d, J =5.95 Hz, 2 H). LCMS (ESI): m/z : $[M + H]$ calcd for $C_{15}H_{16}N_4O$: 269; found 269; RT = 2.835 min.

Example 37. Preparation of 2-(1-aminoisoquinolin-6-yl)piperidine-1-carbonitrile (37)



[0381] A mixture of compound **37.4** (250 mg, 590.60 μ mol, 1 *eq*), tributyl(2-pyridyl)stannane (434.86 mg, 1.18 mmol, 2 *eq*), $\text{Pd(PPh}_3)_2\text{Cl}_2$ (41.45 mg, 59.06 μ mol, 0.10 *eq*) in dioxane (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 10 hour under N_2 atmosphere. TLC (PE: EtOAc=2:1, R_f =0.45) showed the reaction was completed. The reaction mixture was quenched by addition H_2O 50 mL at 25°C, and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=30/1 to 1:1) to give compound **37.3** (200 mg, 474.51 μ mol, 80.34% yield) as a white solid. 1H NMR (400 MHz, chloroform-

d) δ ppm 1.28 - 1.40 (m, 19 H) 7.31 - 7.38 (m, 1 H) 7.70 - 7.98 (m, 3 H) 8.08 (d, $J=8.80$ Hz, 1 H) 8.29 (dd, $J=8.86$, 1.16 Hz, 1 H) 8.43 - 8.57 (m, 2 H) 8.79 (d, $J=4.77$ Hz, 1 H).

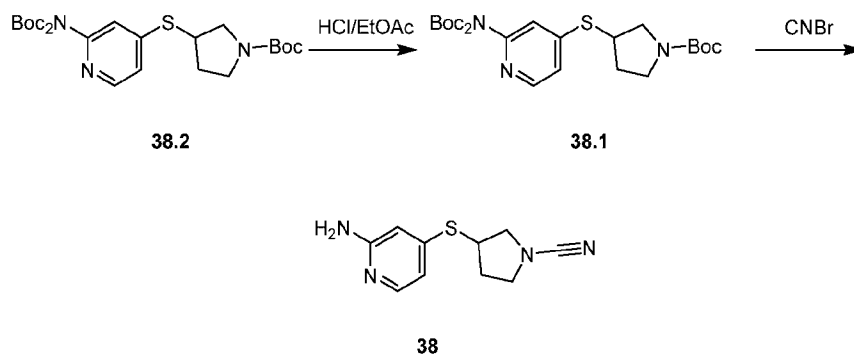
[0382] To a solution of compound **37.3** (200 mg, 474.51 μ mol, 1 *eq*) in MeOH (5 mL) was added PtO₂ (21.55 mg, 94.90 μ mol, 0.20 *eq*). The mixture was stirred under H₂ (50 Psi) at 50 °C for 12 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=30/1 to 1:1) to give compound **37.2** (150 mg, 350.84 μ mol, 73.94% yield) as a white solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.28 (s, 14 H) 1.61 - 1.78 (m, 4 H) 1.94 - 2.04 (m, 2 H) 2.87 (br t, $J=12.13$ Hz, 1 H) 3.23 (br d, $J=12.79$ Hz, 1 H) 3.91 (br d, $J=10.14$ Hz, 1 H) 7.79 (br d, $J=8.60$ Hz, 1 H) 7.87 (d, $J=5.73$ Hz, 1 H) 7.94 (d, $J=8.60$ Hz, 1 H) 8 (s, 1 H) 8.35 (d, $J=5.95$ Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₂₄H₃₃N₃O₄: 428; found 428; RT=0.971 min.

[0383] To a solution of compound **37.2** (150 mg, 350.84 μ mol, 1 *eq*) was added HCl/EtOAc (12.81 mg, 350.84 μ mol, 2 mL, 1 *eq*). The mixture was stirred at 25 °C for 3 hours. The reaction mixture was concentrated under reduced pressure to give compound **37.1** (35 mg, 153.98 μ mol, 43.89% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₄H₁₇N₃: 228; found 228; RT=0.131 min.

[0384] To a solution of compound **37.1** (35 mg, 153.98 μ mol, 1 *eq*) in DMF (1 mL) was added CNBr (16.31 mg, 153.98 μ mol, 11.33 μ L, 1 *eq*) and DIPEA (59.70 mg, 461.94 μ mol, 80.68 μ L, 3 *eq*). The mixture was stirred at 25 °C for 5 min. The residue was purified by prep-HPLC (TFA condition) to give Product **37** (10 mg, 39.63 μ mol, 25.74% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.50 - 1.93 (m, 6 H) 3.28 (td, $J=11.84$, 3.51 Hz, 1 H) 3.49 - 3.57 (m, 1 H) 4.27 (dd, $J=10.52$, 3.07 Hz, 1 H) 6.50 (br s, 2 H) 6.93 (d, $J=5.70$ Hz, 1 H) 7.48 (dd, $J=8.55$, 1.53 Hz, 1 H) 7.70 (s, 1 H) 7.82 (d, $J=5.70$ Hz, 1 H) 8.19 (d, $J=8.77$ Hz, 1 H). LCMS (ESI): *m/z*: [M + H] calcd for C₁₅H₁₆N₄: 253; found 253; RT=2.505 min.

Example 38. Preparation of 3-((2-aminopyridin-4-yl)thio)pyrrolidine-1-carbonitrile (**38**)

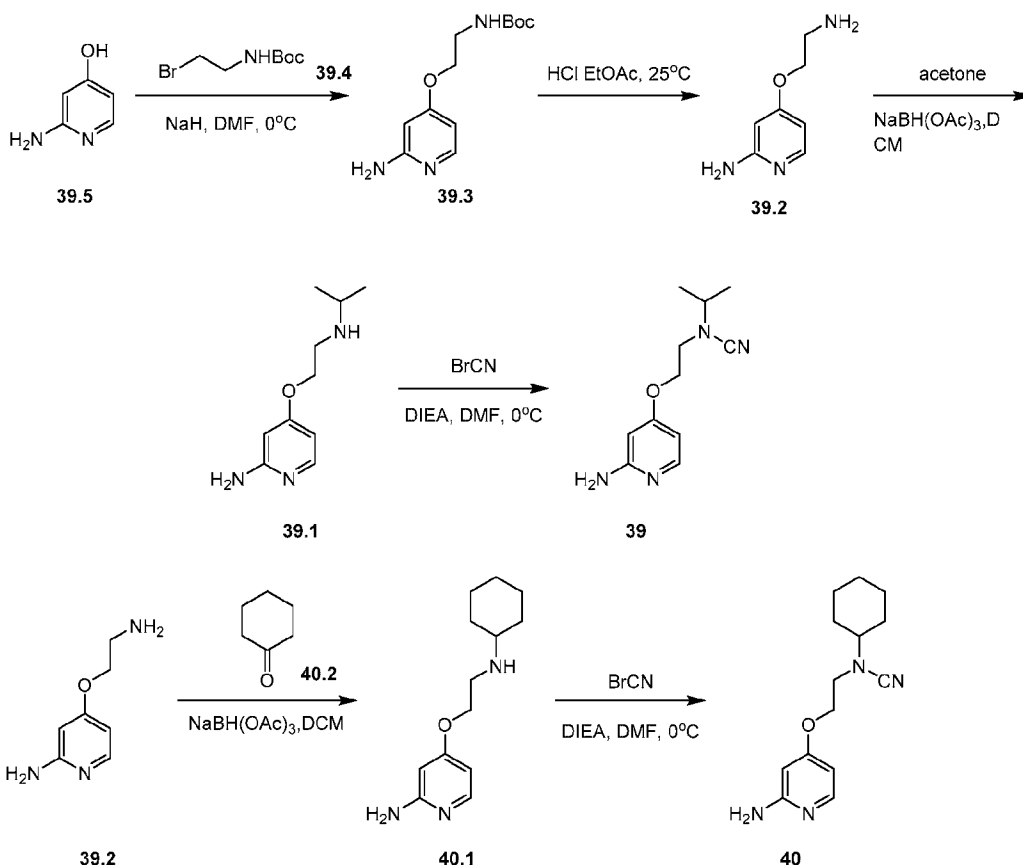
[0385] To a solution of compound **38.2** (90 mg, 181.59 μ mol, 1 *eq*) in HCl/EtOAc (5 mL) at 20°C under N₂. The mixture was stirred at 20 °C for 4 hours. Filtered and concentrated in vacuum to give compound **38.1** (50 mg, 164.11 μ mol, 90.37% yield, 3HCl) as a light yellow solid.



[0386] To a mixture of compound **38.1** (50 mg, 256.04 μmol , 1 eq) and carbononitridic bromide (27.12 mg, 256.04 μmol , 18.83 μL , 1 eq) in DMF (1 mL) was added DIEA (132.36 mg, 1.02 mmol, 178.87 μL , 4 eq) in one portion at 0°C under N_2 . The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (basic condition) to give **Product 38** (4.40 mg, 19.97 μmol , 7.80% yield) as a light yellow oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{S}$: 221; found 221; RT=0.943 min. ^1H NMR (400 MHz, chloroform- d) δ ppm 1.46 (br s, 5 H) 1.90 - 2 (m, 1 H) 2.24 - 2.36 (m, 1 H) 3.32 (dd, J =10.23, 4.71 Hz, 1 H) 3.46 (td, J =8.63, 5.33 Hz, 1 H) 3.53 - 3.62 (m, 1 H) 3.77 (dd, J =10.29, 6.53 Hz, 1 H) 3.86 (quin, J =5.62 Hz, 1 H) 4.38 (br s, 2 H) 6.28 (d, J =1.13 Hz, 1 H) 6.44 (dd, J =5.52, 1.51 Hz, 1 H) 7.87 (d, J =5.52 Hz, 1 H).

Examples 39 and 40. Preparation of *N*-(2-((2-aminopyridin-4-yl)oxy)ethyl)-*N*-isopropylcyanamide (39) and *N*-(2-((2-aminopyridin-4-yl)oxy)ethyl)-*N*-cyclohexylcyanamide (40)

[0387] To a mixture of compound **39.5** (5 g, 45.41 mmol, 1 eq) and compound **39.4** (10.18 g, 45.41 mmol, 1 eq) in DMF (20 mL) was added NaH (2.18 g, 54.49 mmol, 60% purity, 1.20 eq) in portions at 0°C under N_2 . The mixture was stirred at 15 °C for 15 hours. The reaction was monitored by LCMS. After the reaction was completed, water (120 mL) was added dropwise at 0°C. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=10:1 to 2:1) to give compound **39.3** (2.80 g, 11.05 mmol, 24.34% yield) was obtained as a white solid. ^1H NMR (400 MHz, methanol- d_4) ppm 1.45 (s, 9 H), 3.52 (d, J =5.2 Hz, 2H), 4 (t, J =5.2 Hz, 2H), 4.43 (br, 2H), 5.05 (br, 1 H), 5.96 (d, J =1.6, 1 H), 6.25 (dd, J =1.6 Hz, J =6.0 Hz, 1 H), 7.90 (d, J = 6.0 Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{12}\text{H}_{20}\text{N}_3\text{O}_3$: 254; found 254; RT=0.585 min.



[0388] A solution of compound **39.3** (2.80 g, 11.05 mmol, 1 eq) in HCl/MeOH (40 mL) was stirred at 15°C for 2hrs under N₂. The mixture was concentrated in vacuum to give compound **39.2** (2.40 g, crude, HCl salt) was obtained as a white solid.

- 5 [0389] To a mixture of compound **39.2** (400 mg, 2.61 mmol, 1 eq) and acetone (379.16 mg, 6.53 mmol, 479.95 μ L, 2.50 eq) in CH₃CN (10 mL) was added NaBH(OAc)₃ (1.38 g, 6.53 mmol, 2.50 eq) at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins, then added CH₃COOH (31.36 mg, 522 μ mol, 29.87 μ L, 0.20 eq) at 0 °C and stirred for 1 hr. The reaction was monitored by LCMS. Filtered and concentrated in vacuum. Compound **39.1**
- 10 (1.40 g, crude) was obtained as black brown oil. LCMS (ESI): m/z: [M + H] calcd for C₁₀H₁₉N₃O: 196; found 196; RT=0.528 min.

- [0390] To a mixture of compound **39.1** (400 mg, crude) and BrCN (216.98 mg, 2.05 mmol, 150.68 μ L, 1 eq) in DMF (1 mL) was added DIEA (1.06 g, 8.19 mmol, 1.43 mL, 4 eq) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 5 mins. The reaction was
- 15 monitored by LCMS promptly until the reaction was completed. Water (50 mL) was added. The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (5 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in

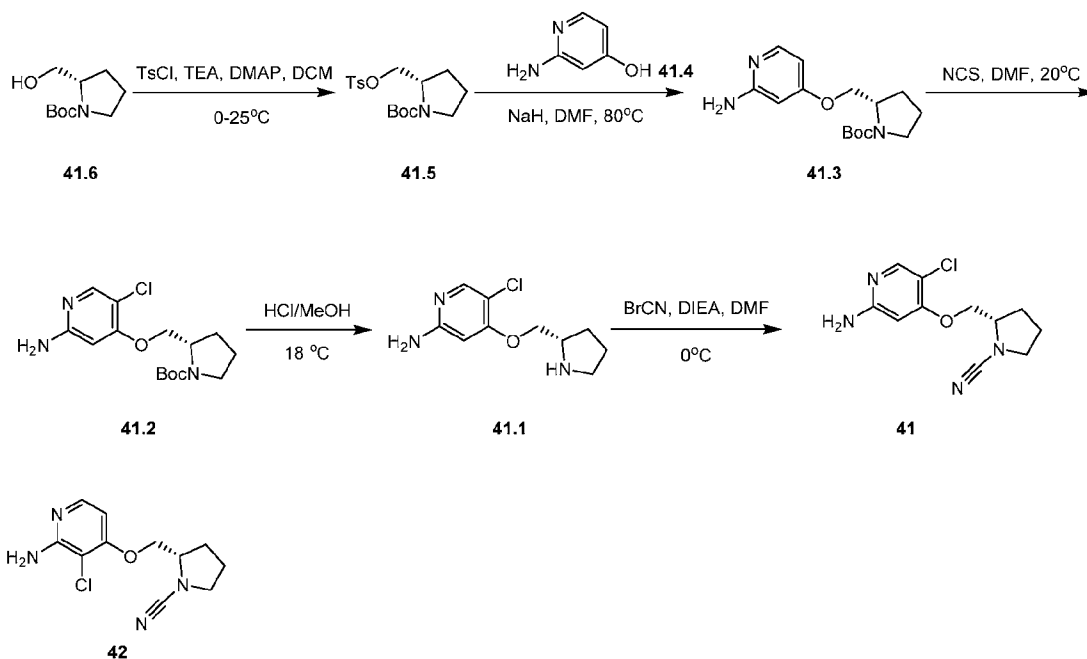
vacuum. The residue was purified by prep-HPLC (basic condition) to give Product **39** (20 mg, 45.40 μ mol, 2.21% yield, 50% purity) was obtained as a colorless oil. ^1H NMR (400 MHz, DMSO- d_6) ppm 1.30 (d, $J=6.4$, 6 H), 3.28 (m, 1 H), 3.42 (t, $J=5.2$ Hz, 2H), 4.16 (t, $J=5.2$ Hz, 2H), 4.68 (br, 2 H) 6.01 (d, $J=2.4$, 1 H), 6.27 (dd, $J=2.4$ Hz, $J=6.0$ Hz, 1 H), 7.89 (d, $J=6.0$ Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{11}\text{H}_{17}\text{N}_4\text{O}$: 221; found 221; RT=2.091 min.

[0391] To a mixture of compound **39.2** (188 mg, 831.49 μ mol, 1 eq, 2HCl) and cyclohexanone **40.2** (244.81 mg, 2.49 mmol, 257.69 μ L, 3 eq) in CH_3CN (5 mL) was added $\text{NaBH}(\text{OAc})_3$ (528.68 mg, 2.49 mmol, 3 eq) in one portion at 0°C under N_2 . The mixture was stirred at 0°C for 30 mins, then added AcOH (9.99 mg, 166.30 μ mol, 9.51 μ L, 0.20 eq) at 0°C and stirred for 1 hours. The reaction was monitored by LCMS. Filtered and concentrated in vacuum to give compound **40.1** (1.40 g, crude) as black brown oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{13}\text{H}_{22}\text{N}_3\text{O}$: 236; found 236; RT=1.159 min.

[0392] To a mixture of compound **40.1** (180 mg, 764.92 μ mol, 1 eq) and BrCN (81.02 mg, 764.92 μ mol, 56.26 μ L, 1 eq) in DMF (1 mL) was added DIEA (395.43 mg, 3.06 mmol, 534.37 μ L, 4 eq) in one portion at 0°C under N_2 . The mixture was stirred at 0°C for 12 mins. The reaction was monitored by LC-MS promptly until the reaction was completed. The residue was purified by prep-HPLC (basic condition) to give product **40** (10 mg, 38.41 μ mol, 5.02% yield) was obtained as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ ppm 1.18-1.30 (m, 3 H), 1.41-1.47 (m, 2 H), 1.64-1.67 (m, 1H), 1.84-1.87 (m, 2H), 1.99-2.02 (m, 2H), 2.82-2.88 (m, 1H), 3.44 (t, $J=4.8$ Hz, 2H), 4.14 (t, $J=4.8$ Hz, 2H), 4.42 (br. s, 2 H), 5.99 (s, 1 H), 6.26 (d, $J=6.0$ Hz, 1 H), 7.92 (d, $J=6.0$ Hz, 1 H). LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{14}\text{H}_{21}\text{N}_4\text{O}$: 261; found 261; RT=2.546 min.

Examples 41 and 42. Preparation of (*S*)-2-(((2-amino-5-chloropyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (41) and (*S*)-2-(((2-amino-3-chloropyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (42)

[0393] To a mixture of compound **41.6** (5 g, 24.84 mmol, 1 eq) and 4-methylbenzenesulfonyl chloride (5.68 g, 29.81 mmol, 1.20 eq) in DCM (50 mL) was added TEA (3.77 g, 37.26 mmol, 5.16 mL, 1.50 eq) and DMAP (485.62 mg, 3.97 mmol, 0.16 eq) in one portion at 0°C under N_2 . The mixture was then heated to 25°C and stirred for 10 hours. The reaction mixture was diluted with H_2O 50 mL and extracted with DCM 90 mL (30 mL x



3). The combined organic layers were washed with brine 60 mL (60 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **41.5** (8.90 g, crude) as a yellow oil. LCMS (ESI): m/z: [M + H] calcd for C₁₇H₂₅NO₅S: 356; found 300; RT=0.890 min.

[0394] To a mixture of compound **41.5** (8.84 g, 24.87 mmol, 1 *eq*) and compound **41.4** (3.01 g, 27.36 mmol, 1.10 *eq*) in DMF (100 mL) was added NaH (895.44 mg, 37.31 mmol, 1.50 *eq*) portionwise at 80°C under N₂. The mixture was stirred at 80°C for 10 hours. The reaction mixture was quenched by addition H₂O 1000 mL, and then extracted with EtOAc 240 mL (80 mL x 3). The combined organic layers were washed with brine 150 mL (150 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH=10:1) to give compound **41.3** (4.50 g, 15.34 mmol, 61.68% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₅H₂₃N₃O₃: 294; found 294; RT=0.692 min.

[0395] To a mixture of compound **41.3** (300 mg, 1.02 mmol, 1 *eq*) in DMF (5 mL) was added NCS (136.20 mg, 1.02 mmol, 1 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 10 hours. The reaction mixture was diluted with H₂O 5 mL and extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **41.2** (100 mg, 305.05 μmol, 29.91% yield) as a colorless oil. LCMS (ESI): m/z:

[M + H] calcd for C₁₅H₂₂ClN₃O₃: 327; found 321 ; RT=0.912 min. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.45 (s, 9 H) 1.81 - 1.93 (m, 1 H) 2.02 - 2.22 (m, 4 H) 3.34 - 3.47 (m, 2 H) 4.13 - 4.23 (m, 2 H) 6.22 (br d, *J*=17.42 Hz, 1 H) 6.49 (br dd, *J*=12.57, 5.51 Hz, 1 H) 7.67 - 7.79 (m, 1 H)

5 [0396] Compound **41.2** (100 mg, 305.05 μmol, 1 *eq*) was added into a solution of HCl/MeOH (5 mL). The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **41.1** (130 mg, crude) as a yellow solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₀H₁₄ClN₃O: 227; found 228; RT=0.096 min.

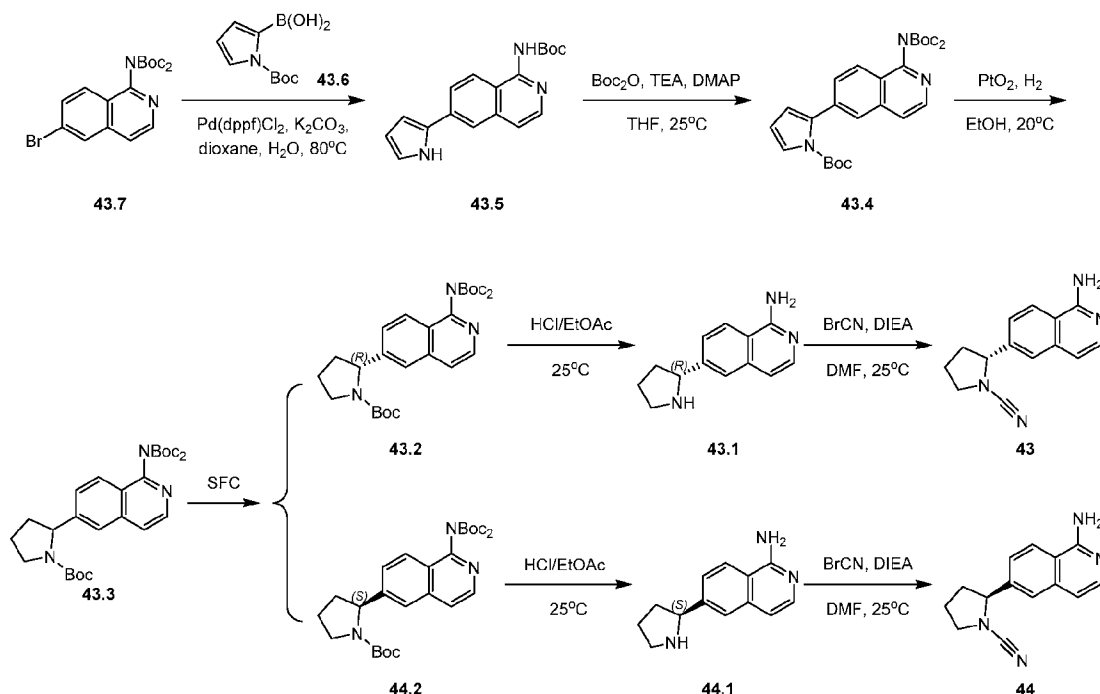
[0397] To a mixture of compound **41.1** (120 mg, 527.03 μmol, 1 *eq*) and DIPEA (272.45 mg, 2.11 mmol, 368.18 μL, 4 *eq*) in DMF (3 mL) was added CNBr (61.41 mg, 579.73 μmol, 42.65 μL, 1.10 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition) to give product **41** (12 mg, 47.49 μmol, 9.01% yield) and product **42** (12 mg, 47.49 μmol, 9.01% yield) as a yellow oil.

[0398] LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₃N₄OCl: 252; found 253; RT=2.314 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.90 - 2.09 (m, 2 H) 2.10 - 2.23 (m, 2 H) 3.43 - 3.52 (m, 1 H) 3.60 (dt, *J*=8.75, 6.23 Hz, 1 H) 3.98 - 4.08 (m, 2 H) 4.09 - 4.16 (m, 1 H) 4.49 (br s, 2 H) 6.02 (s, 1 H) 7.93 (s, 1 H).

[0399] LCMS (ESI): *m/z*: [M + H] calcd for C₁₁H₁₃N₄OCl: 252; found 253; RT=2.226 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.90 - 2.09 (m, 2 H) 2.10 - 2.24 (m, 2 H) 3.42 - 3.54 (m, 1 H) 3.61 (dt, *J*=9, 6.16 Hz, 1 H) 3.99 - 4.06 (m, 1 H) 4.07 - 4.12 (m, 1 H) 4.13 - 4.20 (m, 1 H) 4.86 (br s, 2 H) 6.31 (d, *J*=5.77 Hz, 1 H) 7.90 (d, *J*=5.77 Hz, 1 H).

Examples 43 and 44. Preparation of (*R*)-2-(1-aminoisoquinolin-6-yl)pyrrolidine-1-carbonitrile (43) and (*S*)-2-(1-aminoisoquinolin-6-yl)pyrrolidine-1-carbonitrile (44)

[0400] To a mixture of compound **43.7** (2 g, 4.72 mmol, 1 *eq*), compound **43.6** (996.01 mg, 4.72 mmol, 1 *eq*), K₂CO₃ (3.91 g, 28.32 mmol, 6 *eq*) in dioxane (40 mL) and H₂O (10 mL) was added Pd(dppf)Cl₂ (1.04 g, 1.42 mmol, 0.30 *eq*) in one portion at 15 °C under N₂. The mixture was stirred at 80 °C for 8 hours. The reaction mixture was quenched by addition H₂O 100 mL at 25 °C, and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 3/1) to afford compound **43.4**



(660 mg, 1.30 mmol, 27.54% yield) and compound **43.5** (1 g, 3.23 mmol, 68.48% yield) as brown solid. LCMS (ESI): m/z: compound **43.5**: [M + H] calcd for C₁₈H₁₉N₃O₂:310; found 310; RT=1.775 min; compound **43.4**: [M + H] calcd for C₂₈H₃₅N₃O₆:510; found 510; RT=3.724 min.

[0401] To a mixture of compound **43.5** (1 g, 3.23 mmol, 1 eq) in THF (10 mL) was added Boc₂O (3.53 g, 16.16 mmol, 3.71 mL, 5 eq), TEA (1.31 g, 12.93 mmol, 1.79 mL, 4 eq), DMAP (394.91 mg, 3.23 mmol, 1 eq) in one portion at 15°C under N₂. The mixture was stirred at 15°C for 12 hours. The reaction mixture was diluted with H₂O 50 mL and extracted with EtOAc 120 mL (40 mL x 3). The combined organic layers were washed with brine 20 mL (10 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 3/1) to obtain compound **43.4** (440 mg, 863.44 μmol, 26.71% yield) as brown solid. LCMS (ESI): m/z: [M + H] calcd for C₂₈H₃₅N₃O₆:510; found 510; RT=1.616 min.

[0402] To a mixture of compound **43.4** (1.10 g, 2.16 mmol, 1 eq) in EtOH (30 mL) was added PtO₂ (490.17 mg, 2.16 mmol, 1 eq) in one portion at 15°C under H₂. The mixture was stirred at 15 °C, 50 Psi for 12 hours. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=20/1, 3/1) and future purification by SFC to obtain compound **43.2** (300 mg, 584.08 μmol, 27.04% yield) and compound **44.2** (300 mg, 584.08 μmol, 27.04% yield) as light

yellow oil. LCMS (ESI): m/z: [M + H] calcd for C₂₈H₃₉N₃O₆:514; found 514; RT=1.494 min.

[0403] To a mixture of HCl/EtOAc (4 M, 5 mL) in compound **43.2** (300 mg, 584.08 μmol, 1 eq) in one portion at 15°C. The mixture was stirred at 15 °C for 12 hour. The reaction solution was concentrated in vacuum to obtain compound **43.1** (180 mg, crude, 2HCl) was obtained as light yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₁₃H₁₅N₃:214; found 214; RT=0.177 min.

[0404] To a mixture of compound **43.1** (140 mg, 489.17 μmol, 1 eq, 2HCl) and DIPEA (252.88 mg, 1.96 mmol, 341.73 μL, 4 eq) in DMF (2 mL) was added BrCN (56.99 mg, 538.09 μmol, 39.58 μL, 1.10 eq) at 0°C under N₂. The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition) to give product **4.3** (50 mg, 209.83 μmol, 42.90% yield) was obtained as light yellow solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 7.97 (d, *J*=5.86 Hz, 1 H) 7.82 (d, *J*=8.55 Hz, 1 H) 7.63 (s, 1 H) 7.41 (d, *J*=8.68 Hz, 1 H) 7.05 (d, *J*=5.86 Hz, 1 H) 5.11 (br s, 2 H) 4.82 (t, *J*=7.03 Hz, 1 H) 3.75 - 3.83 (m, 1 H) 3.62 - 3.69 (m, 1 H) 2.43 (dq, *J*=12.65, 6.45 Hz, 1 H) 2.07 (dt, *J*=14.27, 6.98 Hz, 2 H) 1.89 - 1.99 (m, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₄H₁₄N₄:239; found 239; RT=2.035 min.

[0405] To a mixture of compound **44.2** (300 mg, 584.08 μmol, 1 eq) in HCl/EtOAc (4 M, 5 mL) in one portion at 15°C under N₂. The mixture was stirred at 15 °C for 5 hours. The reaction solution was concentrated in vacuum to obtain compound **44.1** (180 mg, crude, 2HCl) was obtained as light yellow solid. LCMS (ESI): m/z: [M + H] calcd for C₁₃H₁₅N₃:214; found 214; RT=10 min.

[0406] To a mixture of compound **44.1** (140 mg, 489.17 μmol, 1 eq, 2HCl), DIPEA (252.88 mg, 1.96 mmol, 341.73 μL, 4 eq) in DMF (2 mL) in one portion at 0°C under N₂. Then added BrCN (56.99 mg, 538.09 μmol, 39.58 μL, 1.10 eq) at 0°C. The mixture was stirred at 0 °C for 10 mins. The residue was purified by prep-HPLC (neutral condition) to give product **44** (40 mg, 167.86 μmol, 34.32% yield) was obtained as light yellow solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 7.98 (d, *J*=5.86 Hz, 1 H) 7.82 (d, *J*=8.55 Hz, 1 H) 7.63 (s, 1 H) 7.41 (d, *J*=8.43 Hz, 1 H) 7.05 (d, *J*=5.86 Hz, 1 H) 5.11 (br s, 2 H) 4.82 (t, *J*=7.03 Hz, 1 H) 3.75 - 3.84 (m, 1 H) 3.62 - 3.70 (m, 1 H) 2.43 (dq, *J*=12.74, 6.42 Hz, 1 H)

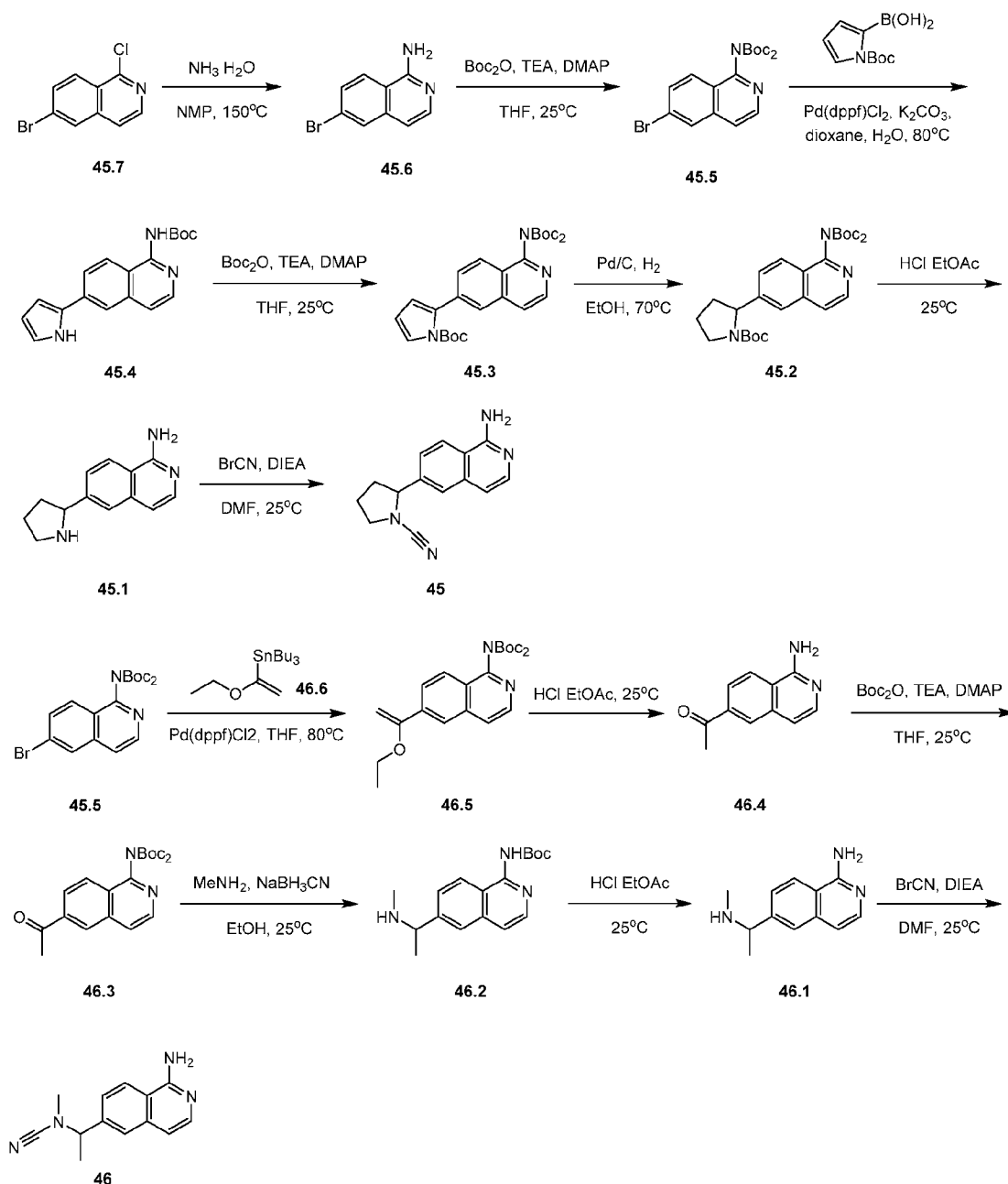
2.03 - 2.13 (m, 2 H) 1.89 - 2 (m, 1 H). LCMS (ESI): m/z: [M + H] calcd for C₁₄H₁₄N₄:239; found 239; RT=2.050 min.

Examples 45 and 46. Preparation of 2-(1-aminoisoquinolin-6-yl)pyrrolidine-1-carbonitrile (45) and N-(1-(1-aminoisoquinolin-6-yl)ethyl)-N-methylcyanamide (46)

5 [0407] To a solution of compound **45.7** (2.50 g, 10.31 mmol, 1 eq) in NMP (20 mL) was added NH₃.H₂O (22.74 g, 648.87 mmol, 24.99 mL, 62.94 eq). The mixture was stirred at 150 °C for 15 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **45.6** (4 g, crude) was obtained as a yellow oil. It was combined with obtained second batch to obtain 8g crude which was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=0:1). The purified compound (2 g, 11.20 mmol, 35.72% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 6.91 (d, *J*=6.14 Hz, 1 H) 7.58 (dd, *J*=8.77, 2.19 Hz, 1 H) 7.75 (d, *J*=5.70 Hz, 1 H) 7.90 (d, *J*=1.75 Hz, 1 H) 8.01 (d, *J*=9.21 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₉H₇N₂Cl: 179; found 179; RT=0.557 min.

[0408] To a solution of compound **45.6** (2 g, 8.97 mmol, 1 eq) in THF (40 mL) was added TEA (3.63 g, 35.86 mmol, 4.97 mL, 4 eq) and Boc₂O (4.89 g, 22.41 mmol, 5.15 mL, 2.50 eq) and DMAP (328.61 mg, 2.69 mmol, 0.30 eq). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O 50 mL at 25°C and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by re-crystallization from ethyl acetate (15 mL) to give the crude product compound **45.5** (2.90 g, 6.85 mmol, 76.38% yield) as yellow solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.30 - 1.34 (m, 1 H) 1.32 (s, 17 H) 7.57 (d, *J*=5.70 Hz, 1 H) 7.71 (dd, *J*=8.77, 1.75 Hz, 1 H) 7.83 (d, *J*=8.77 Hz, 1 H) 8.05 (d, *J*=1.75 Hz, 1 H) 8.45 (d, *J*=5.70 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₉H₂₃BrN₂O₄: 424; found 424; RT=0.962 min.

[0409] To a solution of compound **45.5** (500 mg, 1.18 mmol, 1 eq) and (1-tert-butoxycarbonylpyrrol-2-yl) boronic acid (249 mg, 1.18 mmol, 1 eq) in dioxane (20 mL) and H₂O (5 mL) was added Pd(dppf)Cl₂ (259.03 mg, 354 μmol, 0.30 eq) and K₂CO₃ (489.26 mg, 3.54 mmol, 3 eq). The mixture was stirred at 80 °C for 14 hours. The reaction mixture was



quenched by addition H_2O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=2:1). Compound **45.4** (100 mg, 196.24 μmol , 16.63% yield) was obtained as a yellow oil. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ called for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$: 310; found 310; $\text{RT}=0.734$ min.

[0410] To a solution of compound **45.4** (400 mg, 1.29 mmol, 1 *eq*) in THF (10 mL) was added TEA (522.14 mg, 5.16 mmol, 715.26 μL , 4 *eq*) and Boc_2O (703.86 mg, 3.23 mmol,

- 740.90 μ L, 2.50 *eq*) and DMAP (47.28 mg, 387 μ mol, 0.30 *eq*). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **45.3** (160 mg, 313.98 μ mol, 24.34% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.34 (s, 19 H) 6.28 - 6.33 (m, 1 H) 6.37 (dd, *J*=3.20, 1.65 Hz, 1 H) 7.45 (dd, *J*=3.20, 1.65 Hz, 1 H) 7.58 - 7.68 (m, 2 H) 7.83 (s, 1 H) 7.92 (d, *J*=8.82 Hz, 1 H) 8.43 (d, *J*=5.73 Hz, 1 H).
- 10 **[0411]** To a solution of compound **45.3** (160 mg, 313.98 μ mol, 1 *eq*) in EtOH (5 mL) was added PtO₂ (11 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25°C for 12 hours. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound
- 15 **45.2** (150 mg, 292.04 μ mol, 93.01% yield) was obtained as a yellow oil. LCMS (ESI): *m/z*: [M + H] called for C₂₈H₃₉N₃O₆: 514; found 514; RT=1.672 min.
- [0412]** A mixture of compound **45.2** (150 mg, 292.04 μ mol, 1 *eq*) in HCl/EtOAc (20 mL) was stirred at 25 °C for 14 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **45.1** (80 mg, 279.52 μ mol, 95.71% yield, 2HCl) was obtained as a
- 20 white solid. LCMS (ESI): *m/z*: [M + H] called for C₁₃H₁₅N₃: 214; found 214; RT=0.175 min.
- [0413]** To a solution of compound **45.1** (80 mg, 279.52 μ mol, 1 *eq*, 2HCl) in DMF (2 mL) was added DIEA (144.50 mg, 1.12 mmol, 195.27 μ L, 4 *eq*) and BrCN (32.57 mg, 307.47 μ mol, 22.62 μ L, 1.10 *eq*). The mixture was stirred at 0 °C for 10 min. The residue was purified by prep-HPLC (neutral condition). Product **45** (20 mg, 83.93 μ mol, 30.03% yield)
- 25 was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.84 - 2.02 (m, 1 H) 2.03 - 2.14 (m, 2 H) 2.44 (dq, *J*=12.47, 6.24 Hz, 1 H) 3.57 - 3.70 (m, 1 H) 3.80 (q, *J*=7.78 Hz, 1 H) 7 (d, *J*=5.99 Hz, 1 H) 7.49 (d, *J*=8.68 Hz, 1 H) 7.68 (s, 1 H) 7.75 (d, *J*=5.99 Hz, 1 H) 8.14 (d, *J*=8.68 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] called for C₁₄H₁₄N₄: 239; found 239; RT=2.277 min.
- 30 **[0414]** To a solution of compound **45.5** (500 mg, 1.18 mmol, 1 *eq*) in dioxane (15 mL) was added Pd(PPh₃)₂Cl₂ (82.82 mg, 118 μ mol, 0.10 *eq*) and compound **46.6** (852.31 mg, 2.36

mmol, 796.56 μ L, 2 *eq*). The mixture was stirred at 80 °C for 14 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **46.5** (450 mg, 1.09 mmol, 92.01% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.21 - 1.37 (m, 20 H) 1.50 (br t, *J*=7.02 Hz, 3 H) 3.93 - 4.09 (m, 2 H) 4.43 (br s, 1 H) 4.89 (br s, 1 H) 7.67 (br d, *J*=5.26 Hz, 1 H) 7.88 (q, *J*=8.77 Hz, 2 H) 8.14 (s, 1 H) 8.41 (br d, *J*=5.70 Hz, 1 H). LCMS (ESI): *m/z*: [M + H] called for C₂₃H₃₀N₂O: 415; found 415; RT=0.979 min.

[0415] A mixture of compound **46.5** (450 mg, 1.09 mmol, 1 *eq*) in HCl/EtOAc (10 mL) was degassed and purged with N₂ for 3 times and then the mixture was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **46.4** (230 mg, 1.03 mmol, 94.76% yield, HCl) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.75 (s, 3 H) 7.37 (d, *J*=7.06 Hz, 1 H) 7.65 (d, *J*=7.06 Hz, 1 H) 8.25 (dd, *J*=8.82, 1.32 Hz, 1 H) 8.53 (br d, *J*=6.17 Hz, 2 H).

[0416] To a solution of compound **46.4** (230 mg, 1.24 mmol, 1 *eq*) in THF (5 mL) was added TEA (501.90 mg, 4.96 mmol, 687.54 μ L, 4 *eq*) and Boc₂O (676.58 mg, 3.10 mmol, 712.18 μ L, 2.50 *eq*) and DMAP (45.45 mg, 372 μ mol, 0.30 *eq*). The mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition H₂O 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1). Compound **46.3** (200 mg, 517.54 μ mol, 41.74% yield) was obtained as a yellow solid. LCMS (ESI): *m/z*: [M + H] called for C₂₁H₂₆N₂O₅: 387; found 287; RT=0.626 min.

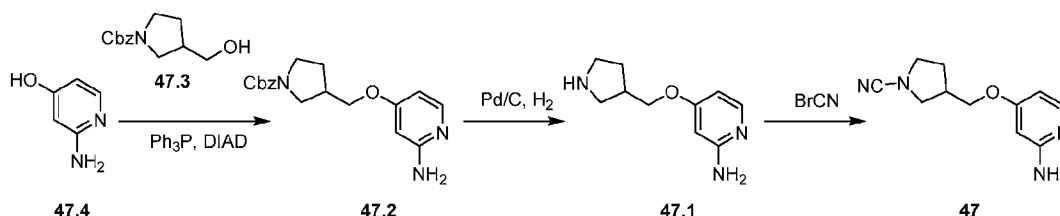
[0417] A mixture of compound **46.3** (100 mg, 258.77 μ mol, 1 *eq*) in MeNH₂ (2 mL) was stirred at 0 °C for 1 hour. To the mixture was added NaBH₃CN (65.04 mg, 1.04 mmol, 4 *eq*) and then added HOAc (23.31 mg, 388.16 μ mol, 22.20 μ L, 1.50 *eq*) make the mixture to pH =4. The mixture was stirred at 25°C for 12 hours. The reaction mixture was quenched by addition saturated NaHCO₃ 20 mL at 25°C make the pH>7 and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (20 mL x 1),

dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 10:1). Compound **46.2** (50 mg, 124.53 μ mol, 48.12% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₂₂H₃₁N₃O₄: 302; found 302; RT=0.565 min.

5 [0418] A mixture of compound **46.2** (50 mg, 165.90 μ mol, 1 *eq*) in HCl/EtOAc (20 mL) was stirred at 25 °C for 13 hours. The mixture was concentrated under reduced pressure to give a residue. Compound **46.1** (45 mg, 164.12 μ mol, 98.93% yield, 2HCl) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₁₂H₁₅N₃: 202; found 202; RT=0.116 min.

[0419] To a solution of compound **46.1** (45 mg, 164.12 μ mol, 1 *eq*, 2HCl) in DMF (2 mL) was added DIEA (84.84 mg, 656.48 μ mol, 114.65 μ L, 4 *eq*) and BrCN (17.38 mg, 164.12 μ mol, 12.07 μ L, 1 *eq*). The mixture was stirred at 0 °C for 10 mins. The residue was purified by prep-HPLC (neutral condition). Product **46** (5 mg, 22.10 μ mol, 13.46% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.67 (d, *J*=7.06 Hz, 3 H) 2.79 (s, 3 H) 4.33 (q, *J*=6.98 Hz, 1 H) 7 (d, *J*=5.95 Hz, 1 H) 7.53 (d, *J*=8.60 Hz, 1 H) 7.68 (s, 1 H) 7.76 (d, *J*=5.95 Hz, 1 H) 8.16 (d, *J*=8.60 Hz, 1 H). LCMS (ESI): m/z: [M + H] called for C₁₃H₁₄N₄: 227; found 227; RT=2.247 min.

Example 47. Preparation of 3-(((2-aminopyridin-4-yl)oxy)methyl)pyrrolidine-1-carbonitrile (47)



20 [0420] To a solution of compound **47.4** (800 mg, 7.27 mmol, 1 *eq*) in DCM (40 mL) was added compound **47.3** (1.71 g, 7.27 mmol, 1 *eq*), PPh₃ (2.86 g, 10.90 mmol, 1.50 *eq*) and DIAD (2.20 g, 10.90 mmol, 2.12 mL, 1.50 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 25°C for 16 hours. The reaction mixture was added water 20 mL, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1:1).

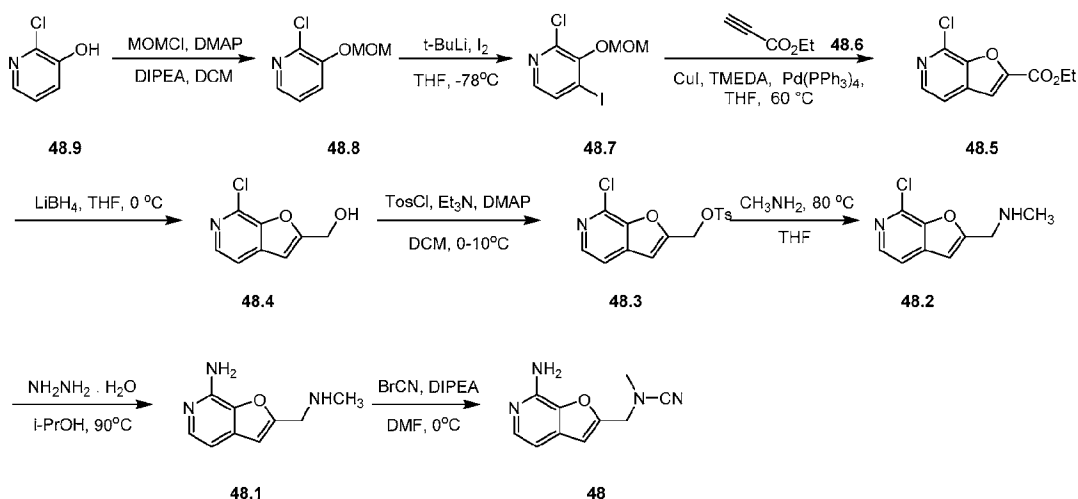
25 Compound **47.2** (700 mg, 2.14 mmol, 29.45% yield) was obtained as a white solid. ¹H NMR (400 MHz, chloroform-*d*) ppm 2.06 - 2.10 (m, 1 H) 2.66 - 2.72 (m, 1 H) 3.27 - 3.29 (m, 1 H)

3.46 - 3.68 (m, 3 H) 3.87 - 3.94 (m, 5 H) 4.43 (s, 2 H) 5.15 (s, 2 H) 5.95 (d, J=2.0 Hz, 1 H)
6.24 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.30 - 7.37 (m, 5 H) 7.89 (d, J=6.0 Hz, 1 H).

[0421] H₂ was bubbled into a solution of compound **47.2** (400 mg, 1.22 mmol, 1 *eq*) and H₂ in MeOH (40 mL) at 25°C under 50 psi for 10 hours. The reaction mixture was filtered, the
5 filter was concentrated under reduced pressure to remove solvent. Compound **47.1** (200 mg, 1.03 mmol, 84.83% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, methanol-d₄) ppm 1.58 - 1.63 (m, 1 H) 2.02 - 2.04 (m, 1 H) 2.60 - 2.79 (m, 2 H) 2.94 - 3.14 (m, 3 H) 3.91 - 3.98 (m, 2 H) 6.09 (d, J=2.0 Hz, 1 H) 6.23 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.69 (d, J=6.4 Hz, 1 H).

[0422] To a solution of compound **47.1** (100 mg, 517.46 μmol, 1 *eq*) in THF (5 mL) was added DIEA (133.75 mg, 1.03 mmol, 180.75 μL, 2 *eq*) and BrCN (54.81 mg, 517.46 μmol, 38.06 μL, 1 *eq*) in turn at 0°C under N₂. The resulting mixture was stirred at 0°C for 1 hour. The reaction mixture was added water 10 mL, extracted with EtOAc (10mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and
15 concentrated under reduced pressure to give a residue. The residue was purified by p-TLC (SiO₂, Ethyl acetate = 0:1). Product **47** (14 mg, 64.15 μmol, 12.40% yield) was obtained as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₁H₁₄N₄O:218; found 219; RT=2.522 min. ¹H NMR (400 MHz, chloroform-d) ppm 1.85 - 1.88 (m, 1 H) 2.12 - 2.17 (m, 1 H) 2.73 - 2.75 (m, 1 H) 3.32 - 3.35 (m, 1 H) 3.50 - 3.63 (m, 3 H) 3.92 - 3.98 (m, 2 H) 5 (s, 2 H) 6.04 (s, 1 H)
20 6.27 (dd, J=6.0 Hz, 2.0 Hz, 1 H) 7.85 (d, J=6.0 Hz, 1 H).

Example 48. Preparation of *N*-((7-aminofuro[2,3-*c*]pyridin-2-yl)methyl)-*N*-methylcyanamide (48**)**



[0423] To a solution of compound **48.9** (10 g, 77.20 mmol, 1 eq) in DCM (100 mL) was added chloro(methoxy)methane (7.46 g, 92.64 mmol, 7.04 mL, 1.20 eq) and DMAP (1.51 g, 12.35 mmol, 0.16 eq) and DIPEA (19.95 g, 154.40 mmol, 26.96 mL, 2 eq) at 0°C. The mixture was stirred at 10°C for 12 hours. The reaction mixture was diluted with H₂O 30 mL and extracted with DCM 90 mL (30 mL x 3). The combined organic layers were washed with brine 30 mL (30 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 3:1) to give compound **48.8** (13.20 g, 76.04 mmol, 98.50% yield) as a colorless solid. LCMS (ESI): m/z: [M + H] calcd for C₇H₈ClNO₂: 173; found 174; RT=0.937 min. ¹H NMR (400 MHz, chloroform-d) δ ppm 3.51 (s, 3 H) 5.23 - 5.30 (m, 2 H) 7.18 (dd, J=8.11, 4.60 Hz, 1 H) 7.47 (dd, J=8.11, 1.53 Hz, 1 H) 8.04 (dd, J=4.82, 1.32 Hz, 1 H).

[0424] To a solution of compound **48.8** (4.40 g, 25.35 mmol, 1 eq) in THF (130 mL) was added dropwise t-BuLi (1.3 M, 48.74 mL, 2.50 eq) at -78°C. The mixture was stirred at -78°C for 1 hour. Then I₂ (11.58 g, 45.62 mmol, 9.19 mL, 1.80 eq) was added above mixture at -78°C. The mixture was stirred at 10°C for 12 hours. The reaction mixture was quenched by addition H₂O 10 mL at 0°C, and then diluted with H₂O 50 mL and extracted with EtOAc 150 mL (50 mL x 3). The combined organic layers were washed with brine 50 mL (50 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 3:1) to give compound **48.7** (12.80 g, 42.74 mmol, 56.21% yield) as a yellow solid. ¹H NMR (400 MHz, chloroform-d) δ ppm 3.68 - 3.82 (m, 3 H) 5.18 - 5.27 (m, 2 H) 7.70 (d, J=5.01 Hz, 1 H) 7.80 (d, J=5.01 Hz, 1 H).

[0425] To a solution of compound **48.7** (3.90 g, 13.02 mmol, 1 eq) in THF (100 mL) was added ethyl compound **48.6** (1.53 g, 15.63 mmol, 1.53 mL, 1.20 eq) and TMEDA (18.01 g, 154.96 mmol, 23.39 mL, 11.90 eq). The mixture was degassed with N₂ for 10 mins. Then the mixture was added CuI (496.01 mg, 2.60 mmol, 0.20 eq) and Pd(PPh₃)₄ (3.01 g, 2.60 mmol, 0.20 eq). Then the mixture was stirred at 60 °C for 15 hours. The reaction mixture was diluted with H₂O 40 mL and extracted with EtOAc 180 mL (60 mL x 3). The combined organic layers were washed with brine 60 mL (60 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=20/1 to 5:1) to give compound **48.5** (940 mg, 4.17 mmol, 16.01% yield) as a white solid.

[0426] To a solution of compound **48.5** (710 mg, 3.15 mmol, 1 *eq*) in THF (2 mL) was added LiBH₄ (102.80 mg, 4.72 mmol, 1.50 *eq*) and stirred at 0 °C for 12 hours. The reaction mixture was diluted with H₂O 15 mL and extracted with EtOAc 45 mL (15 mL x 3). The combined organic layers were washed with brine 15 mL (15 mL x 1), dried over Na₂SO₄,
5 filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2/1 to 1:1) to give compound **48.4** (300 mg, 1.63 mmol, 51.88% yield) as a colorless solid. LCMS (ESI): *m/z*: [M + H] calcd for C₈H₆ClNO₂:183; found 184; RT=0.593 min.

[0427] To a solution of compound **48.4** (150 mg, 817.04 μmol, 1 *eq*) in DCM (2 mL) was
10 added TosCl (186.92 mg, 980.45 μmol, 1.20 *eq*), DMAP (19.96 mg, 163.41 μmol, 0.20 *eq*) and Et₃N (248.03 mg, 2.45 mmol, 339.76 μL, 3 *eq*) at 0°C. The mixture was stirred at 10°C for 2 hours. The reaction mixture was diluted with H₂O 10 mL and extracted with DCM 30mL (10 mL x 3). The combined organic layers were washed with brine 10 mL (10mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **48.3**
15 (130 mg, crude) as a yellow solid. LCMS (ESI): *m/z*: [M + H] calcd for C₁₅H₁₂ClNO₄S:337; found 338; RT=0.842 min.

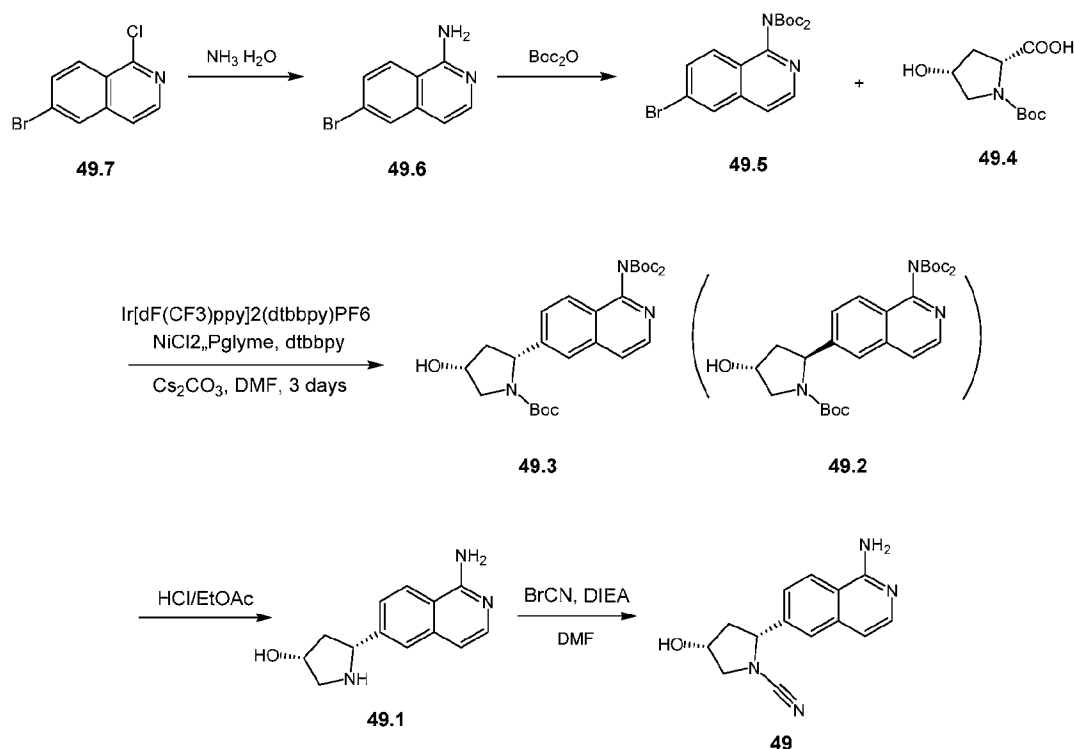
[0428] To a solution of compound **48.3** (130 mg, 384.87 μmol, 1 *eq*) in THF (2 mL) was added MeNH₂ (11.95 mg, 384.87 μmol, 2 mL, 1 *eq*). The mixture was stirred at 80 °C for 12 hours. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc 30 mL
20 (10 mL x 3). The combined organic layers were washed with brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **48.2** (50 mg, crude) as a yellow oil. LCMS (ESI): *m/z*: [M + H] calcd for C₉H₉ClN₂O:196; found 197; RT=0.152 min.

[0429] To a solution of compound **48.2** (50 mg, 254.28 μmol, 1 *eq*) in i-PrOH (7 mL) was
25 added NH₂NH₂.H₂O (2.40 g, 48.01 mmol, 2.33 mL, 188.80 *eq*). The mixture was stirred at 90 °C for 72 hours. The reaction mixture was concentrated under reduced pressure to remove solvent to give compound **48.1** (60 mg, crude) as a yellow oil.

[0430] To a solution of compound **48.1** (60 mg, 338.60 μmol, 1 *eq*) in DMF (2 mL) was
30 added BrCN (35.86 mg, 338.60 μmol, 24.91 μL, 1 *eq*) and DIPEA (131.28 mg, 1.02 mmol, 176.93 μL, 3 *eq*). The mixture was stirred at 0 °C for 0.2 hour. The residue was purified by prep-HPLC to give product **48** (2 mg, 9.89 μmol, 2.92% yield) as a colorless oil. LCMS

(ESI): m/z : $[M + H]$ calcd for $C_{10}H_{10}N_4O$:202; found 203; $RT=2.484$ min. 1H NMR (400 MHz, methanol- d_4) δ ppm 2.95 (s, 3 H) 4.43 (s, 2 H) 6.75 - 6.98 (m, 2 H) 7.69 (d, $J=5.62$ Hz, 1 H).

Example 49. Preparation of (2*R*,4*R*)-2-(1-aminoisoquinolin-6-yl)-4-hydroxypyrrolidine-1-carbonitrile (49)



[0431] To a solution of compound **49.7** (1.5 g, 6.19 mmol, 1 *eq*) in NMP (15 mL) was added $NH_3 \cdot H_2O$ (54.58 g, 389.32 mmol, 15 mL, 25% purity, 62.94 *eq*). The mixture was stirred at 150 °C for 15 hours. The reaction mixture was quenched by addition of H_2O (500 mL) at 25 °C and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with saturated brine 50 mL (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , DCM: MeOH = 10:1) to give compound **49.6** (1.6 g, 7.17 mmol, 38.65% yield) as yellow oil.

[0432] To a solution of compound **49.6** (1.6 g, 7.17 mmol, 1 *eq*) in THF (20 mL) was added Boc_2O (6.26 g, 28.69 mmol, 6.59 mL, 4 *eq*) dropwise at 18 °C under N_2 . Then to the mixture was added TEA (3.63 g, 35.86 mmol, 4.99 mL, 5 *eq*) and DMAP (140.20 mg, 1.15 mmol, 0.16 *eq*). This mixture was stirred at 18 °C for 10 hours. The reaction mixture was

concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **49.5** (1.1 g, 2.60 mmol, 36% yield) as a white solid. LCMS (ESI) m/z: [M + H] calcd for C₇H₈N₂O₂: 423; found 424; RT=1.501 min.

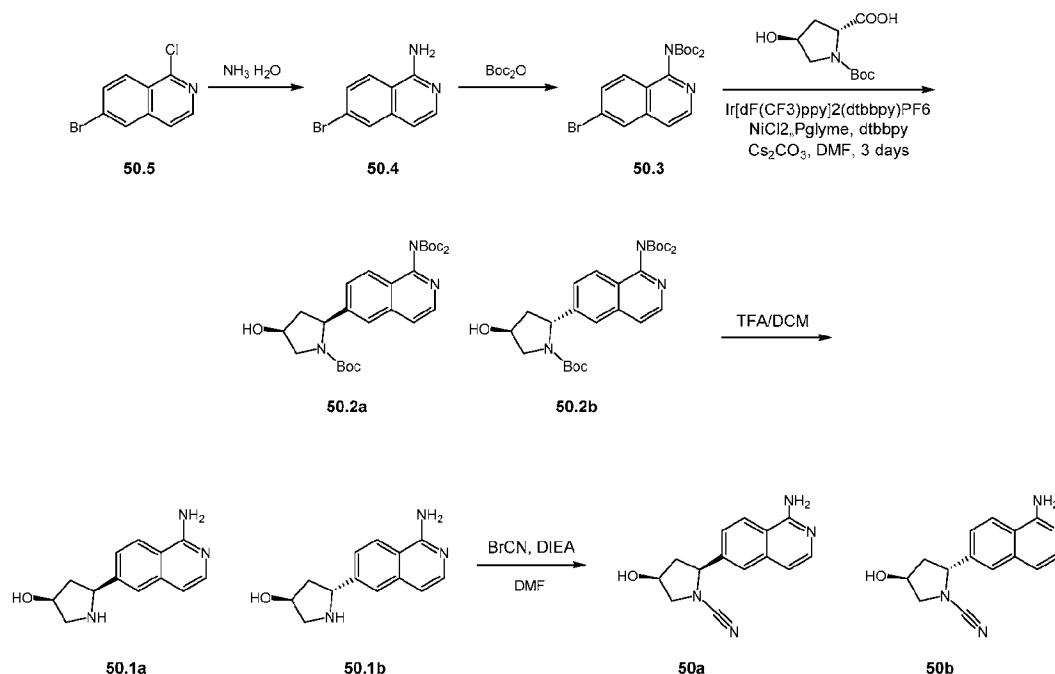
- 5 **[0433]** To a mixture of compound **49.5** (1.1 g, 2.60 mmol, 1 *eq*), compound **49.4** (901.38 mg, 3.90 mmol, 1.5 *eq*), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (2.81 mg, 26 μmol, 0.01 *eq*), NiCl₂.Pglyme (56.31 mg, 259.86 μmol, 0.1 *eq*), dtbbpy (104.08 mg, 389.79 μmol, 0.15 *eq*) in DMF (40 mL) was added Cs₂CO₃ (1.27 g, 3.90 mmol, 1.5 *eq*) in one portion in the glovebox. Then the mixture was irradiated with two 34 W fluorescent lamps for 72 hours at 25 °C. The
10 residue was purified by prep-HPLC (TFA conditions) to give compound **49.2** (60 mg, 113.3 μmol, 4.4% yield) and compound **49.3** (100 mg, 188.8 μmol, 7.3% yield) as yellow solid.

[0434] Compound **49.3** (100 mg, 188.81 μmol, 1 *eq*) was dissolved into HCl/EtOAc (10 mL), the mixture was stirred at 15 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **49.1** (60 mg, crude) as a white solid.

- 15 **[0435]** To a mixture of compound **49.1** (60 mg, 261.7 μmol, 1 *eq*) and cyanogen bromide (27.7 mg, 261.7 μmol, 19.25 μL, 1 *eq*) in DMF (1 mL) was added DIPEA (101.5 mg, 785.5 μmol, 136.75 μL, 3 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 10 mins. The residue was purified by prep-HPLC (neutral conditions) to give **49**, (4 mg, 15.7 μmol, 6 % yield) as a white solid. LCMS (ESI) m/z: [M + H] calcd. for C₁₄H₁₄N₄O: 254;
20 found 255; RT=1.77 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.88 - 1.99 (m, 1 H), 2.47 - 2.58 (m, 1 H), 3.57 (d, J=10.51 Hz, 1 H), 4 (dd, J=10.51, 3.91 Hz, 1 H), 4.52 (br s, 1 H), 5.59 (dd, J=10.09, 6.42 Hz, 1 H), 7.13 (d, J=6.24 Hz, 1 H), 7.55 - 7.61 (m, 1 H), 7.82 (d, J=6.36 Hz, 2 H) and 8.12 (d, J=8.44 Hz, 1 H) ppm.

- Examples 50a and 50b. Preparation of (2*S*,4*S*)-2-(1-aminoisoquinolin-6-yl)-4-hydroxypyrrolidine-1-carbonitrile (50a) and (2*R*,4*S*)-2-(1-aminoisoquinolin-6-yl)-4-hydroxypyrrolidine-1-carbonitrile (50b)**
25

- [0436]** To a solution of compound **50.5** (1.5 g, 6.19 mmol, 1 *eq*) in NMP (15 mL) was added NH₃.H₂O (54.58 g, 389.32 mmol, 15 mL, 63 *eq*). The mixture was stirred at 150 °C for 15 hours. The reaction mixture was quenched by addition H₂O (500 mL) at 25 °C and
30 extracted with EtOAc (500 mL x 3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under



reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, DCM: MeOH = 10:1) to give compound **50.4** (1.6 g, 7.17 mmol, 39% yield) as yellow oil.

- 5 **[0437]** To a solution of compound **50.4** (1.6 g, 7.17 mmol, 1 *eq*) in THF (20 mL) was added Boc₂O (6.26 g, 28.69 mmol, 6.59 mL, 4 *eq*) dropwise at 18 °C under N₂. Then the mixture was added TEA (3.63 g, 35.86 mmol, 4.99 mL, 5 *eq*) and DMAP (140.2 mg, 1.15 mmol, 0.16 *eq*), and stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column
- 10 chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **50.3** (1.5 g) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for C₇H₈N₂O₂: 423; found 424; RT=1.501 min.

- [0438]** To a mixture of compound **50.3** (1.5 g, 3.54 mmol, 1 *eq*), (2R,4S)-1-tert-butoxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylic acid (1.23 g, 5.32 mmol, 1.5 *eq*),
- 15 Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (3.83 mg, 35.44 μmol, 0.01 *eq*), NiCl₂.Pglyme (76.79 mg, 354.36 μmol, 0.1 *eq*), dtbbpy (141.92 mg, 531.54 μmol, 0.15 *eq*) in DMF (40 mL) was added Cs₂CO₃ (1.73 g, 5.32 mmol, 1.5 *eq*) in one portion in the glovebox. Then the mixture was irradiated with two 34 W fluorescent lamps for 72 hours at 25 °C. The residue was purified by prep-HPLC (TFA condition) to give compound **50.2a** (100 mg, 188.81 μmol, 5% yield)
- 20 and compound **50.2b** (100 mg, 188.81 μmol, 5% yield) as yellow solid.

[0439] To a solution of compound **50.2a** (100 mg, 188.81 μmol , 1 *eq*) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **50.1a** (110 mg) as a white solid. ¹H NMR (400 MHz, METHANOL-d₄) δ : 2.41 - 2.62 (m, 2 H), 3.38 - 3.46 (m, 1 H), 3.67 - 3.77 (m, 2 H), 4.76 (br t, J=3.75 Hz, 1 H), 5.19 (br dd, J=11.91, 6.39 Hz, 1 H), 7.25 (d, J=7.06 Hz, 1 H), 7.63 (d, J=7.06 Hz, 1 H), 7.88 (dd, J=8.71, 1.65 Hz, 1 H), 8.02 - 8.10 (m, 1 H) and 8.54 (d, J=8.82 Hz, 1 H) ppm.

[0440] To a mixture of compound **50.1a** (110 mg, 192.53 μmol , 1 *eq*) and cyanogen bromide (20.39 mg, 192.53 μmol , 14.16 μL , 1 *eq*) in DMF (1 mL) was added DIPEA (74.65 mg, 577.58 μmol , 100.6 μL , 3 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 10 mins. The residue was purified by prep-HPLC (neutral condition) to give **50a** (5 mg, 19.66 μmol , 10% yield) as a white solid. LCMS (ESI) m/z: [M + H] calcd for C₁₄H₁₅N₄O: 255; found 255; RT=1.787 min. ¹H NMR (400 MHz, METHANOL-d₄) δ : 1.98 - 2.09 (m, 1 H), 2.38 (dd, J=13.59, 6.14 Hz, 1 H), 3.52 (d, J=10.52 Hz, 1 H), 3.98 (dd, J=10.52, 3.51 Hz, 1 H), 4.52 (br s, 1 H), 5.06 (dd, J=10.52, 6.14 Hz, 1 H), 7.01 (d, J=6.14 Hz, 1 H), 7.54 (dd, J=8.77, 1.75 Hz, 1 H), 7.74 (dd, J=3.73, 1.97 Hz, 2 H) and 8.17 (d, J=8.77 Hz, 1 H) ppm.

[0441] To a solution of compound **50.2b** (100 mg, 188.81 μmol , 1 *eq*) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **50.1b** (110 mg, crude) as a white solid. ¹H NMR (400 MHz, METHANOL-d₄) δ : 2.46 - 2.55 (m, 1 H), 2.58 - 2.68 (m, 1 H), 3.40 - 3.49 (m, 1 H), 3.68 (dd, J=12.24, 3.86 Hz, 1 H), 4.79 (br t, J=3.64 Hz, 1 H), 5.66 (br dd, J=11.69, 6.39 Hz, 1 H), 7.46 - 7.54 (m, 1 H), 7.69 - 7.76 (m, 1 H), 7.84 - 7.93 (m, 1 H), 8.19 - 8.27 (m, 1 H) and 8.52 - 8.60 (m, 1 H) ppm.

[0442] To a mixture of compound **50.1b** (110 mg, 192.53 μmol , 1 *eq*, 3 TFA) and cyanogen bromide (20.39 mg, 192.53 μmol , 14.16 μL , 1 *eq*) in DMF (1 mL) was added DIPEA (74.65 mg, 577.58 μmol , 100.6 μL , 3 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 mins. The residue was purified by semi-preparative scale HPLC (TFA condition) to give **50b** (5 mg, 19.7 μmol , 10% yield) as a white solid. LCMS (ESI) m/z: [M + H] calcd for C₁₄H₁₅N₄O: 255; found 255; RT=1.779 min. ¹H NMR (400 MHz, METHANOL-d₄) δ : 1.94 (ddd, J=13.48, 9.98, 4.17 Hz, 1 H), 2.53 (dd, J=13.59, 6.58 Hz, 1 H), 3.53 - 3.60 (m, 1 H), 4 (dd, J=10.74, 3.73 Hz, 1 H), 4.52 (br s, 1 H), 5.60 (dd,

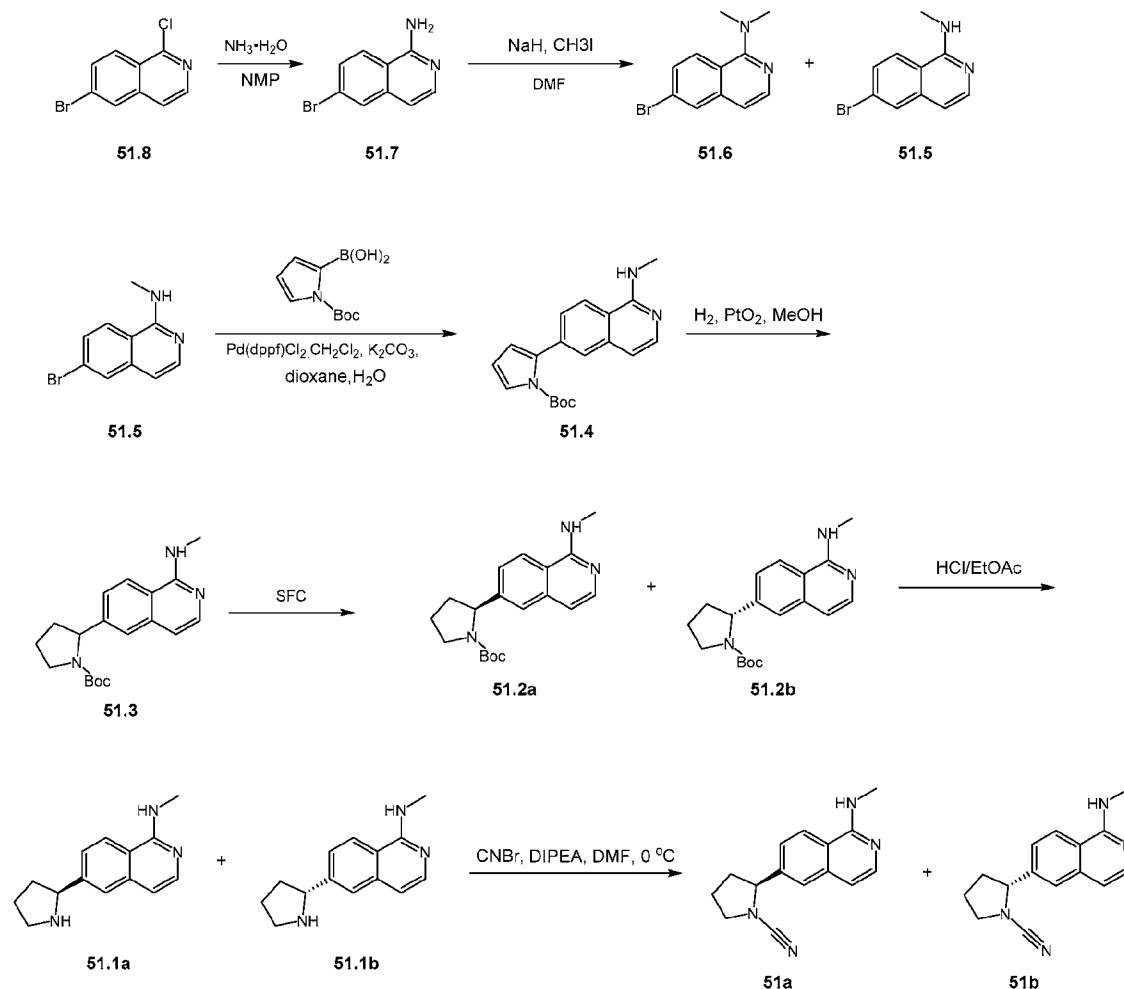
J=10.09, 6.58 Hz, 1 H), 7.14 (d, J=6.58 Hz, 1 H), 7.58 (t, J=7.89 Hz, 1 H), 7.80 - 7.87 (m, 2 H) and 8.13 (d, J=8.33 Hz, 1 H) ppm.

Examples 51a and 51b. Preparation of (*S*)-2-(1-(methylamino)isoquinolin-6-yl)pyrrolidine-1-carbonitrile (51a) and (*R*)-2-(1-(methylamino)isoquinolin-6-yl)pyrrolidine-1-carbonitrile (51b)

[0443] To a solution of compound **51.8** (2.5 g, 10.31 mmol, 1 *eq*) in NMP (30 mL) was added NH₃.H₂O (30 mL, 33% aqueous solution) in one portion at 150 °C under N₂. The mixture was stirred at 150 °C for 10 hours. The reaction mixture was diluted with H₂O (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:2) to give compound **51.7** (35 g, 95% yield) as a white solid. LCMS (ESI) m/z: [M + H] calcd for C₉H₈BrN₂: 223; found 223; RT=0.761 min.

[0444] To a solution of compound **51.7** (7 g, 31.4 mmol, 1 *eq*) in DMF (70 mL) was added NaH (1.26 g, 31.4 mmol, 60% suspension in mineral oil, 1 *eq*) portion-wise at 0 °C under N₂. The mixture was stirred at 0 °C for 30 mins, then the mixture was added CH₃I (6.68 g, 47.1 mmol, 2.93 mL, 1.5 *eq*) in one portion, and heated to 25 °C and stirred for 1.5 hours. The reaction mixture was quenched by addition of H₂O (70 mL) and then was extracted with EtOAc (70 mL x 3). The combined organic layers were washed with H₂O (70 mL x 3), and then with brine (70 mL), dried over Na₂SO₄, filtered and concentrated. This residue was purified by medium pressure liquid chromatography (MPLC) (SiO₂, petroleum ether/ethyl acetate=10/1 to 0:1) to give compound **51.5** (2.8 g, 11.81 mmol, 38% yield) as an orange solid and to give compound **51.6** (1.09 g, 4.34 mmol, 14% yield) as yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ: 8.03 (d, J=5.70 Hz, 1 H), 7.82 (d, J=1.75 Hz, 1 H), 7.56 - 7.61 (m, 1 H), 7.47 - 7.53 (m, 1 H), 6.82 (d, J=5.70 Hz, 1 H), 5.33 (br s, 1 H), 3.58 (s, 1 H) and 3.15 (d, J=4.82 Hz, 3 H) ppm.

[0445] A mixture of compound **51.5** (2.7 g, 11.4 mmol, 1 *eq*), N-(t-butoxycarbonyl)pyrrole-2-boronic acid (2.64 g, 12.53 mmol, 1.1 *eq*), Pd(dppf)Cl₂.CH₂Cl₂ (2.79 g, 3.42 mmol, 0.3 *eq*), K₂CO₃ (9.44 g, 68.33 mmol, 6 *eq*) in dioxane (28 mL) and H₂O (7 mL) was degassed and purged with N₂ 3 times; then the mixture was stirred at 80 °C for 5 hour under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (15 mL) and then extracted with EtOAc (15 mL x 3). The combined organic layers were washed with



saturated brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO₂, petroleum ether/ethyl acetate=10/1 to 1:1) to give compound **51.4** (3.6 g, 11.13 mmol, 98% yield) as a yellow solid.

- 5 LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₉H₂₂N₃O₂: 324; found 324; RT=0.974 min. ¹H NMR (400 MHz, chloroform-*d*) δ: 8.03 (d, *J*=5.95 Hz, 1 H), 7.62 - 7.72 (m, 2 H), 7.37 - 7.49 (m, 1 H), 7.37 - 7.49 (m, 1 H), 7.37 - 7.49 (m, 1 H), 7.26 (s, 2 H), 6.89 - 6.95 (m, 1 H), 6.92 (d, *J*=5.95 Hz, 1 H), 6.23 - 6.34 (m, 2 H), 5.27 (br s, 1 H), 3.18 (d, *J*=4.85 Hz, 3 H) and 1.34 (s, 9 H) ppm.

- 10 **[0446]** To a solution of compound **51.4** (3.60 g, 11.13 mmol, 1 *eq*) in MeOH (400 mL) was added PtO₂ (252.79 mg, 1.11 mmol, 0.1 *eq*) under N₂. The suspension was degassed under vacuum and purged with hydrogen gas several times, then was stirred under H₂ (50 psi) at 50 °C for 10 hours. The reaction mixture was filtered; the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO₂, petroleum ether/ethyl acetate=10/1 to 1:1) to give compound **51.3** (1.8 g, 4.64 mmol, 38% yield, 84.4%
- 15

purity) as a white solid. LCMS (ESI) m/z : $[M + H]$ calcd for $C_{19}H_{26}N_3O_2$: 328; found 328; RT=0.899 min. 1H NMR (400 MHz, chloroform- d) δ : 8.02 (br d, $J=5.38$ Hz, 1 H), 7.69 (br d, $J=8.56$ Hz, 1 H), 7.43 (d, $J=1.34$ Hz, 1 H), 7.29 (br d, $J=1.22$ Hz, 1 H), 6.88 (d, $J=5.87$ Hz, 1 H), 5.31 (br s, 1 H), 4.79 - 5.12 (m, 1 H), 3.69 (br s, 2 H), 3.17 (br d, $J=4.28$ Hz, 3 H), 2.39 (br s, 1 H), 1.80 - 2 (m, 4 H) and 1.09 - 1.60 (m, 11 H) ppm.

[0447] 500 mg of compound **51.3** was purified by SFC (column: Chiral Pak IC-H 250 x 30 μ m; mobile phase: [0.1% NH_3 in H_2O / ETOH]; B%: 40%-40%, 8min) to give compound **51.2a** (188 mg) and compound **51.2b** (229 mg) as white solid.

[0448] To compound **51.2a** (188 mg, 574.18 μ mol, 1 *eq*) was added HCl/EtOAc (4 M, 18.6 mL) the reaction mixture was stirred at 25 $^{\circ}C$ for 12h. The reaction mixture was concentrated under reduced pressure to give compound **51.1a** (180 mg) as a hydrogen chloride salt. 1H NMR (400 MHz, METHANOL- d_4) δ : 8.51 (d, $J=8.68$ Hz, 1 H), 8.06 (s, 1 H), 7.89 (br d, $J=8.44$ Hz, 1 H), 7.63 (d, $J=6.85$ Hz, 1 H), 7.26 (d, $J=6.85$ Hz, 1 H), 3.45 - 3.66 (m, 2 H), 3.24 (s, 3 H), 2.63 (br d, $J=8.07$ Hz, 1 H) and 2.16 - 2.40 (m, 3 H) ppm.

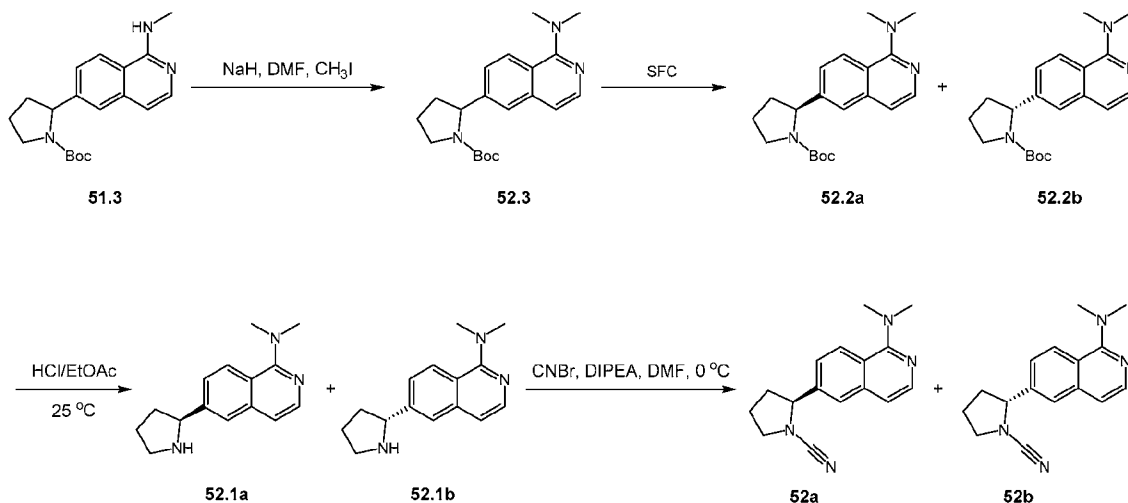
[0449] To a solution of **51.1a** (30 mg, 113.74 μ mol, 1 *eq*) in DMF (1 mL) was added cyanogen bromide (12.05 mg, 113.74 μ mol, 8.37 μ L, 1 *eq*) and DIPEA (29.4 mg, 227.48 μ mol, 39.62 μ L, 2 *eq*). The mixture was stirred at 0 $^{\circ}C$ for 1h. The reaction mixture was filtered, and the organic layers has the desired compound. The residue was purified by semi-preparative scale HPLC (column: Agela Durashell C18 150 x 25 5 μ m; mobile phase: [water (10mM NH_4HCO_3)-ACN]; B%: 20%-60%, 10 min) to give **51a** (5 mg, 19.4 μ mol, 17% yield, 97.9% purity) as a yellow solid. LCMS (ESI) m/z : $[M + H]$ calcd for $C_{15}H_{17}N_4$: 253; found 253; RT=2.357 min. 1H NMR (400 MHz, METHANOL- d_4) δ : 8.10 (d, $J=8.60$ Hz, 1 H), 7.82 (d, $J=6.17$ Hz, 1 H), 7.67 (d, $J=1.54$ Hz, 1 H), 7.48 (dd, $J=8.60$, 1.76 Hz, 1 H), 6.92 (d, $J=5.73$ Hz, 1 H), 4.83 - 4.88 (m, 1 H), 3.81 (dt, $J=8.93$, 7.22 Hz, 1 H), 3.65 (ddd, $J=8.93$, 7.39, 5.73 Hz, 1 H), 3.06 (s, 2 H), 2.45 (dq, $J=12.43$, 6.29 Hz, 1 H), 2.04 - 2.15 (m, 2 H) and 1.89 - 1.99 (m, 1 H) ppm.

[0450] To compound **51.2b** (229 mg, 699.41 μ mol, 1 *eq*) was added HCl/EtOAc (4 M, 22.7 mL) the reaction mixture was stirred at 25 $^{\circ}C$ for 12 h. The reaction mixture was concentrated under reduced pressure to give compound **51.1b** (289 mg) as a hydrogen chloride salt. 1H NMR (400 MHz, METHANOL- d_4) δ : 8.50 (d, $J=8.68$ Hz, 1 H), 8.05 (d, $J=1.47$ Hz, 1 H), 7.89 (dd, $J=8.68$, 1.83 Hz, 1 H), 7.63 (d, $J=6.97$ Hz, 1 H), 7.26 (d, $J=6.97$

Hz, 1 H), 3.44 - 3.62 (m, 2 H), 3.24 (s, 3 H), 2.58 - 2.67 (m, 1 H) and 2.21 - 2.37 (m, 3 H) ppm.

[0451] To a solution of compound **51.1b** (30 mg, 113.74 μ mol, 1 *eq*) in DMF (1 mL) was added cyanogen bromide (12.05 mg, 113.74 μ mol, 8.37 μ L, 1 *eq*) and DIPEA (29.40 mg, 227.48 μ mol, 39.62 μ L, 2 *eq*). The mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered, and the organic layers were concentrated. The residue was purified by semi-preparative scale HPLC (column: Agela Durashell C18 150 x 25 5 μ ; mobile phase: [water (10 mM NH₄HCO₃)-ACN]; B%: 20%-60%, 10 min) to give **51b** (5 mg, 19.7 μ mol, 17% yield, 99.4% purity) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for C₁₅H₁₇N₄: 253; found 253; RT=2.357 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 8.10 (d, *J*=8.77 Hz, 1 H), 7.82 (d, *J*=6.14 Hz, 1 H), 7.66 (d, *J*=1.75 Hz, 1 H), 7.48 (dd, *J*=8.77, 1.75 Hz, 1 H), 6.92 (d, *J*=6.14 Hz, 1 H), 4.82 - 4.87 (m, 1 H), 3.75 - 3.86 (m, 1 H), 3.60 - 3.71 (m, 1 H), 3.05 (s, 3 H), 2.38 - 2.50 (m, 1 H), 2.04 - 2.17 (m, 2 H) and 1.89 - 1.99 (m, 1 H) ppm.

Examples 52a and 52b. Preparation of (*S*)-2-(1-(dimethylamino)isoquinolin-6-yl)pyrrolidine-1-carbonitrile (**52a**) and (*R*)-2-(1-(dimethylamino)isoquinolin-6-yl)pyrrolidine-1-carbonitrile (**52b**)



[0452] To a solution of compound **51.3** (800 mg, 2.44 mmol, 1 *eq*) in DMF (8 mL) was added NaH (134.97 mg, 3.37 mmol, 60% purity, 1.38 *eq*) portion-wise at 0 °C under N₂. The mixture was stirred at 0 °C for 30 mins, then to the mixture was added CH₃I (478.59 mg, 3.37 mmol, 209.91 μ L, 1.38 *eq*) in one portion, and the mixture was heated to 25 °C and stirred for 15.5 hours. The reaction mixture was quenched by addition H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with H₂O (10 mL x 3), and

the combined organic layers were washed with saturated brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO₂, petroleum ether/ethyl acetate=10/1 to 1:1) to give compound **52.3** (480 mg, 1.33 mmol, 54% yield, 94.4% purity) as yellow oil. LCMS (ESI) m/z: [M + H] calcd for C₂₀H₂₈N₃O₂: 342; found 342; RT=1.170 min. ¹H NMR (400 MHz, chloroform-*d*) δ: 8.06 (br d, *J*=8.60 Hz, 3 H), 7.46 (s, 1 H), 7.30 (br d, *J*=8.82 Hz, 2 H), 7.10 (d, *J*=5.73 Hz, 2 H), 4.91 (br s, 1 H), 3.68 (br s, 3 H), 3.09 (br s, 9 H), 2.38 (br s, 2 H), 1.91 (br t, *J*=6.06 Hz, 5 H), 1.46 (br s, 5 H) and 1.13 (br s, 9 H) ppm.

[0453] Compound **52.3** was purified by SFC (column: Chiral Pak AY-H 250 x 30 5μ; mobile phase, A: 0.1% NH₃H₂O in IPA; B: 30%-30%, 5 min) to give compound **52.2a** (180 mg) and compound **52.2b** (200 mg) as white solid.

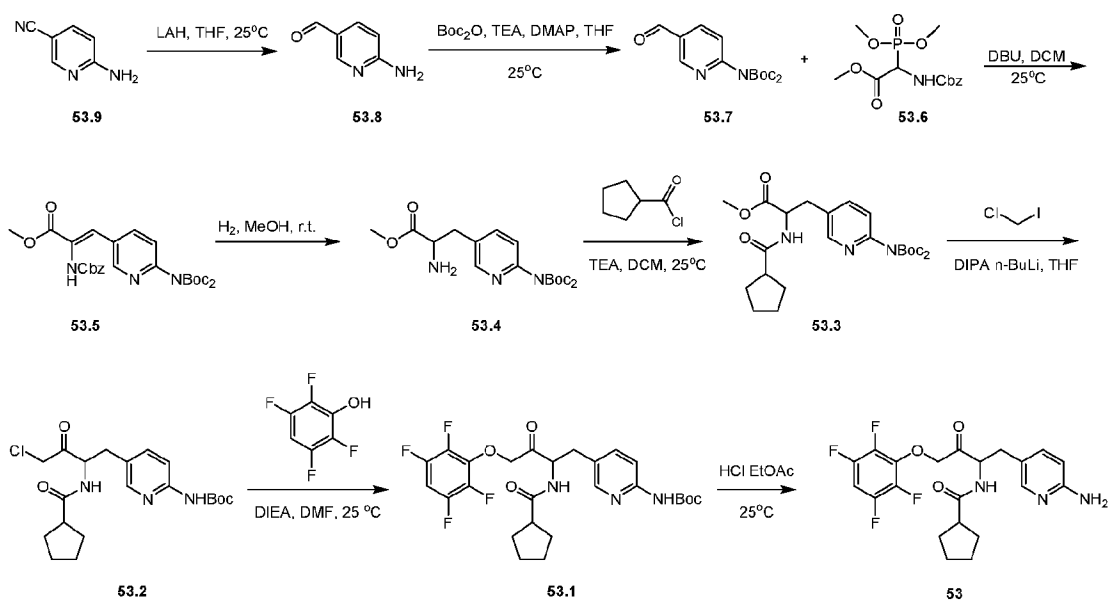
[0454] To compound **52.2a** (180 mg, 527.17 μmol, 1 *eq*) was added HCl/EtOAc (4 M, 6 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give to give compound **52.1a** (189 mg) as a hydrogen chloride salt. ¹H NMR (400 MHz, METHANOL-*d*₄) δ: 8.62 (d, *J*=8.80 Hz, 1 H), 8.14 (d, *J*=1.59 Hz, 1 H), 7.91 (dd, *J*=8.86, 1.77 Hz, 1 H), 7.71 (d, *J*=6.85 Hz, 1 H), 7.43 (d, *J*=6.85 Hz, 1 H), 3.60 (s, 6 H), 3.33 (dt, *J*=3.24, 1.68 Hz, 2 H), 2.60 - 2.73 (m, 1 H), 2.24 - 2.45 (m, 3 H) and 2.04 (s, 1 H) ppm.

[0455] To a solution of compound **52.1a** (30 mg, 108 μmol, 1 *eq*, HCl) in DMF (1 mL) was added cyanogen bromide (11.44 mg, 108 μmol, 7.94 μL, 1 *eq*) and DIPEA (27.91 mg, 215.99 μmol, 37.62 μL, 2 *eq*). The mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered, and the organic layers were concentrated. The residue was purified by semi-preparative scale HPLC (column: Agela Durashell C18 150 x 25 5μ; mobile phase A: [water (10mM NH₄HCO₃)-ACN]; B: 25%-65%, 10min) to give **52a** (7 mg, 25.42 μmol, 24% yield, 96.7% purity) as a white solid. LCMS (ESI) m/z: [M + H] calcd for C₁₆H₁₉N₄:267; found 267; RT=2.628 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ: 8.21 (d, *J*=8.82 Hz, 1 H), 7.97 (d, *J*=5.95 Hz, 1 H), 7.76 (d, *J*=1.54 Hz, 1 H), 7.53 (dd, *J*=8.82, 1.76 Hz, 1 H), 7.25 (d, *J*=5.73 Hz, 1 H), 4.87 - 4.90 (m, 1 H), 3.81 (dt, *J*=8.82, 7.28 Hz, 1 H), 3.65 (ddd, *J*=9.04, 7.28, 5.73 Hz, 1 H), 3.10 (s, 5 H), 3.04 - 3.14 (m, 1 H), 2.39 - 2.50 (m, 1 H), 2.03 - 2.14 (m, 2 H) and 1.94 (dq, *J*=12.49, 7.60 Hz, 1 H) ppm.

[0456] To compound **52.2b** (200 mg, 585.7 μ mol, 1 *eq*) was added HCl/EtOAc (4 M, 6 mL). The reaction mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give compound **52.1b** (203 mg) as a hydrogen chloride salt. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 8.57 - 8.62 (m, 1 H), 8.10 - 8.13 (m, 1 H), 7.85 - 7.91 (m, 1 H), 7.65 - 7.70 (m, 1 H), 7.37 - 7.43 (m, 1 H), 3.57 (s, 6 H), 3.34 (s, 1 H), 2.56 - 2.74 (m, 1 H) and 2.18 - 2.42 (m, 3 H) ppm.

[0457] To a solution of compound **52.1b** (30 mg, 108 μ mol, 1 *eq*) in DMF (1 mL) was added cyanogen bromide (11.44 mg, 108 μ mol, 7.94 μ L, 1 *eq*) and DIPEA (27.91 mg, 216 μ mol, 37.62 μ L, 2 *eq*). The mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered, and the organic layers were concentrated to give the residue. The residue was purified by semi-preparative scale HPLC (column: Agela Durashell C18 150 x 25, 5 μ ; mobile phase: [water (10mM NH₄HCO₃)-ACN]; B%: 25%-65%, 10min) to give **52b** (7 mg, 26 μ mol, 24% yield, 99.8% purity) as a white solid. LCMS (ESI) *m/z*: [M + H] calcd for C₁₆H₁₉N₄: 267; found 267; RT=2.621 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 8.22 (d, *J*=8.77 Hz, 1 H), 7.98 (d, *J*=5.70 Hz, 1 H), 7.76 (s, 1 H), 7.54 (dd, *J*=8.55, 1.97 Hz, 1 H), 7.26 (d, *J*=6.14 Hz, 1 H), 4.90 (br s, 1 H), 3.78 - 3.86 (m, 1 H), 3.61 - 3.70 (m, 1 H), 3.10 (s, 6 H), 2.42 - 2.49 (m, 1 H), 2.05 - 2.15 (m, 1 H) and 1.92 - 2 (m, 1 H) ppm.

Example 53. Preparation of N-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)cyclopentanecarboxamide (53)



[0458] To a solution of compound **53.9** (10 g, 83.95 mmol, 1 *eq*) in THF (150 mL) was added LAH (6.37 g, 167.90 mmol, 2 *eq*) at 0°C. The mixture was stirred at 0°C for 1.5 hours. The reaction mixture was quenched by addition saturated sodium sulfate at 0 °C and added 100 ml H₂O then extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated brines (30 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the product compound **53.8** (7.50 g, 61.42 mmol, 73.16% yield) as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₆H₆N₂O: 123; found 123; RT=0.099 min.

[0459] To a solution of compound **53.8** (7.50 g, 61.42 mmol, 1 *eq*) in THF (100 mL) was added TEA (24.86 g, 245.68 mmol, 34.05 mL, 4 *eq*), Boc₂O (40.21 g, 184.26 mmol, 42.33 mL, 3 *eq*) and DMAP (1.50 g, 12.28 mmol, 0.20 *eq*). The mixture was stirred at 25 °C for 1.5 hours. The reaction mixture was quenched by addition H₂O 100 mL at 25°C and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated brines (50 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1). Compound **53.7** (1.2 g, 3.72 mmol, 6.06% yield) was obtained as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.42 - 1.61 (m, 21 H) 7.66 (d, *J*=8.38 Hz, 1 H) 8.19 (dd, *J*=8.60, 2.21 Hz, 1 H) 8.87 (d, *J*=2.21 Hz, 1 H) 9.98 - 10.13 (m, 1 H).

[0460] To a solution of compound **53.7** (1.03 g, 3.10 mmol, 1 *eq*) in DCM (20 mL) was added DBU (708.40 mg, 4.65 mmol, 701.39 μL, 1.50 *eq*). The mixture was stirred at 25 °C for 0.5 hr. Then to the mixture was added compound **53.6** (1 g, 3.10 mmol, 1 *eq*), the mixture was stirred at 25 °C for 0.5 hr. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1). Compound **53.5** (1 g, 1.90 mmol, 61.15% yield) was obtained as a yellow oil. LCMS (ESI): m/z: [M + H] called for C₂₇H₃₃N₃O₈: 528; found 528; RT=0.917 min.

[0461] To a solution of compound **53.5** (1 g, 1.90 mmol, 1 *eq*) in MeOH (10 mL) was added Pd-C (10%, 0.3 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25°C for 15 hours. The reaction mixture was filtered and the filter was concentrated. Compound **53.4** (1 g, crude) was obtained as a yellow oil. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.35 - 1.54 (m, 23 H) 2.83 - 3.13 (m, 2 H) 3.70 - 3.77 (m, 4 H) 7.19 (d, *J*=8.16 Hz, 1 H) 7.61 (dd, *J*=8.16, 2.43

Hz, 1 H) 8.33 (d, $J=2.21$ Hz, 1 H). LCMS (ESI): m/z : $[M + H]$ called for $C_{19}H_{29}N_3O_6$: 396; found 396; RT=0.701 min.

[0462] To a solution of compound **53.4** (600 mg, 1.52 mmol, 1 *eq*) in DCM (10 mL) was added TEA (307.06 mg, 3.03 mmol, 420.63 μ L, 2 *eq*) and cyclopentanecarbonyl chloride (241.41 mg, 1.82 mmol, 221.48 μ L, 1.20 *eq*). The mixture was stirred at 25 °C for 5 mins. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1). Compound **53.3** (650 mg, 1.32 mmol, 86.99% yield) was obtained as a yellow oil. LCMS (ESI): m/z : $[M + H]$ called for $C_{25}H_{37}N_3O_7$: 492; found 492; RT=0.866min.

[0463] To a solution of DIPA (349.94 mg, 3.46 mmol, 486.03 μ L, 5 *eq*) in THF (5 mL) was added *n*-BuLi (2.5 M, 1.38 mL, 5 *eq*). The mixture was stirred at 0°C for 0.5 hr under N₂. Then the mixture was added to the solution of compound **53.3** (340 mg, 691.0 μ mol, 1 *eq*) and chloriodomethane (609.96 mg, 3.46 mmol, 251.01 μ L, 5 *eq*) in THF (5 mL) was stirred at -78°C for 0.5 hr. The reaction mixture was quenched by addition saturated NH₄Cl (20 ml) at 25°C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with saturated Na₂SO₃ (10 mL) and saturated NaHCO₃ (10 mL) and saturated brines (10mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Compound **53.2** (500 mg, crude) was obtained as a yellow oil. LCMS (ESI): m/z : $[M + H]$ called for $C_{20}H_{28}N_3O_4Cl$: 410; found 410; RT=0.805min.

[0464] To a solution of compound **53.2** (500 mg, 1.22 mmol, 1 *eq*) in DMF (5 mL) was added DIEA (472.93 mg, 3.66 mmol, 639.10 μ L, 3 *eq*) and 2, 3, 5, 6-tetrafluorophenol (303.85 mg, 1.83 mmol, 1.50 *eq*). The mixture was stirred at 25°C for 15 hours. The reaction mixture was quenched by addition saturated NaHCO₃ 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (10 mL x 1), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (TFA condition). Compound **53.1** (50 mg, 74.14 μ mol, 6.08% yield, 80% purity) was obtained as a yellow solid. LCMS (ESI): m/z : $[M + H]$ called for $C_{26}H_{29}N_3O_5F_4$: 540; found 540; RT=1.310min.

[0465] The solution of compound **53.1** (50 mg, 92.67 μ mol, 1 *eq*) in HCl/EtOAc (2 mL) was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition). Product **53** (5 mg, 11.38 μ mol, 12.28% yield) was obtained as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ

ppm 1.31 - 1.77 (m, 8 H) 2.34 (dt, $J=3.69$, 1.79 Hz, 1 H) 2.67 - 2.71 (m, 1 H) 3.01 (dd, $J=14.11$, 4.41 Hz, 1 H) 4.60 (ddd, $J=10.20$, 8.10, 4.63 Hz, 1 H) 5.22 (d, $J=2.21$ Hz, 2 H) 6.89 (d, $J=9.04$ Hz, 1 H) 7.61 (tt, $J=10.91$, 7.28 Hz, 1 H) 7.71 (d, $J=1.54$ Hz, 1 H) 7.79 (br d, $J=9.04$ Hz, 2 H) 8.27 (d, $J=8.16$ Hz, 1 H). LCMS (ESI): m/z : [M + H] calcd for

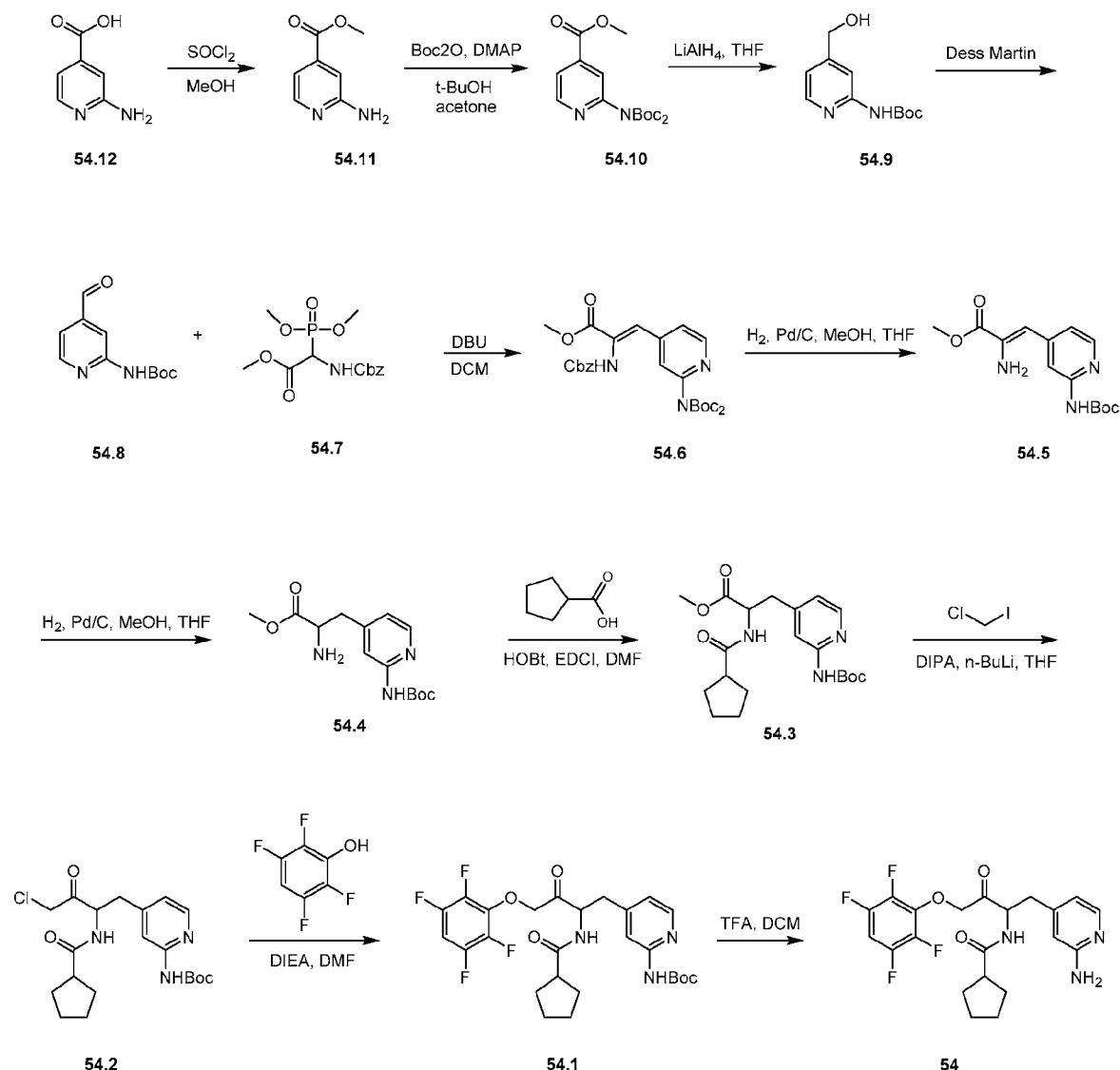
5 C₂₁H₂₁N₃O₃F₄: 440; found 440; RT=2.662 min.

Example 54. Preparation of *N*-(1-(2-aminopyridin-4-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)cyclopentanecarboxamide (54)

[0466] To a solution of compound **54.12** (58 g, 419.92 mmol, 1 eq) in MeOH (600 mL) was added SOCl₂ (99.92 g, 839.84 mmol, 60.93 mL, 2 eq) dropwise at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins, then was heated to 18°C and stirred at 18°C for 14.5 hours. The reaction mixture was concentrated under reduced pressure to give compound **54.11** (65 g, crude) as a white solid. LCMS (ESI): m/z : [M + H] calcd for C₁₇H₁₈N₂O₂: 152; found 153; RT=0.100 min.

[0467] To a mixture of methyl compound **54.11** (65 g, 427.21 mmol, 1 eq) and DMAP (2.61 g, 21.36 mmol, 0.05 eq) in t-BuOH (500 mL) and ACETONE (150 mL) was added Boc₂O (279.72 g, 1.28 mol, 294.44 mL, 3 eq) dropwise at 18°C under N₂. The mixture was stirred at 18 °C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to obtain compound **54.10** (110 g, 312.16 mmol, 73.07% yield) as a white solid. LCMS (ESI): m/z : [M + H] calcd for C₁₇H₂₄N₂O₆: 352; found 353; RT=0.877 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.39 - 1.50 (m, 19 H) 3.97 (s, 3 H) 7.77 (dd, $J=5.02$, 1.38 Hz, 1 H) 7.82 (s, 1 H) 8.62 (d, $J=5.02$ Hz, 1 H).

[0468] To a solution of compound **54.10** (60 g, 170.27 mmol, 1 eq) in THF (1 L) was added LiAlH₄ (12.92 g, 340.54 mmol, 2 eq) portionwise at 0°C under N₂. The mixture was stirred at 0 °C for 1 hours, then heated to 18 °C and stirred at 18 °C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H₂O 1000 mL and extracted with EtOAc 1500 mL (500 mL x 3). The combined organic layers were washed with brine 1000 mL (1000 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **54.9** (15 g, 66.89 mmol, 39.28% yield) as a white solid. LCMS (ESI): m/z : [M + H] calcd for C₁₁H₁₆N₂O₃: 293; found 294; RT=0.313 min.



[0469] To a solution of compound **54.9** (8 g, 35.67 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (18.16 g, 42.81 mmol, 13.25 mL, 1.20 *eq*) portionwise at 18°C under N_2 . The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H_2O 60 mL and extracted with DCM 150 mL (50 mL x 3). The combined organic layers were washed with brine 100 mL (100 mL x 1), 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/Ethyl acetate=5:1) to give compound **54.8** (5.10 g, 22.95 mmol, 64.33% yield) as a white solid. ^1H NMR (400 MHz, chloroform-*d*) δ ppm 1.59 (s, 9 H) 7.41 (dd, J =5.08, 1.32 Hz, 1 H) 8.48 (s, 1 H) 8.52 (d, J =5.15 Hz, 1 H) 8.83 (br s, 1 H).

[0470] To a solution of compound **54.7** (1.49 g, 4.50 mmol, 1 *eq*) in DCM (15 mL) was added DBU (1.03 g, 6.75 mmol, 1.02 mL, 1.50 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 0.5 hour, then to the mixture was added compound **54.8** (1 g, 4.50 mmol, 1 *eq*) in one portion at 18 °C, then was stirred at 18 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **54.6** (1.90 g, 4.44 mmol, 98.78% yield) as a white solid.

[0471] To a solution compound **54.6** (1 g, 2.34 mmol, 1 *eq*) in MeOH (50 mL) and THF (50 mL) was added Pd-C (10%, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 20 °C for 15 hours. The reaction mixture was filtered and concentrated under reduced pressure to give compound **54.5** (700 mg, crude) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₄H₁₉N₃O₄: 293; found 294; RT=0.638 min.

[0472] To a solution of compound **54.5** (600 mg, 2.05 mmol, 1 *eq*) in MeOH (50 mL) and THF (50 mL) was added Pd-C (10%, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50psi) at 20 °C for 15 hours. The reaction mixture was filtered and concentrated under reduced pressure to give compound **54.4** (600 mg, crude) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₄H₂₁N₃O₄: 295; found 296; RT=0.239 min.

[0473] To a mixture of cyclopentanecarboxylic acid (193.24 mg, 1.69 mmol, 184.04 µL, 1 *eq*) and EDCI (357.01 mg, 1.86 mmol, 1.10 *eq*) in DMF (10 mL) was added HOBt (251.64 mg, 1.86 mmol, 1.10 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then the mixture was added dropwise a solution of compound **54.4** (500 mg, 1.69 mmol, 1 *eq*) in DMF (5 mL), then the mixture was added dropwise DIPEA (656.42 mg, 5.08 mmol, 887.05 µL, 3 *eq*) and stirred at 0 °C for 1 hour. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with brine 15 mL (15 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **54.3** (600 mg, 1.53 mmol, 90.69% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₂₀H₂₉N₃O₅: 391; found 392; RT=0.681 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.43 - 1.62 (m, 9 H) 1.66 - 1.93 (m, 5 H) 2.49 - 2.62 (m, 1 H) 3.02 - 3.12 (m, 1 H) 3.14 - 3.25 (m, 1 H) 3.71 - 3.87 (m, 2

H) 4.86 - 5 (m, 1 H) 5.96 (br d, $J=7.53$ Hz, 1 H) 6.72 (d, $J=5.02$ Hz, 1 H) 7.77 (s, 1 H) 8 (s, 1 H) 8.16 (d, $J=5.02$ Hz, 1 H).

[0474] To a solution of DIPA (426.51 mg, 4.21 mmol, 592.38 μ L, 5.50 eq) in THF (6 mL) was added n-BuLi (2.5 M, 1.69 mL, 5.50 eq) at 0°C, the mixture was stirred at 0 °C for 30 mins. The mixture was added to a solution of compound **54.3** (300 mg, 766.36 μ mol, 1 eq) and chloriodomethane (675.85 mg, 3.83 mmol, 278.13 μ L, 5 eq) in THF (6 mL) at -78°C. The mixture was stirred at -78°C for 30 mins. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl 5 mL, and then extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with sat. aq. Na₂SO₃ 10 mL (10 mL x 1), and brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **54.2** (400 mg, crude) as a white solid.

[0475] To a mixture of compound **54.2** (400 mg, 975.82 μ mol, 1 eq) and 2,3,5,6-tetrafluorophenol (243.08 mg, 1.46 mmol, 1.50 eq) in DMF (5 mL) was added DIEA (504.46 mg, 3.90 mmol, 681.70 μ L, 4 eq) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 10 hours. The residue was purified by prep-HPLC (neutral condition) to give compound **54.1** (60 mg, 111.21 μ mol, 11.40% yield) as a yellow solid. LCMS (ESI): m/z : [M + H] calcd for C₂₆H₂₉N₃O₅F₄: 539; found 540; RT=1.306 min.

[0476] To a solution of compound **54.1** (60 mg, 111.21 μ mol, 1 eq) in DCM (10 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 242.90 eq) in one portion at 18°C under N₂. The mixture was stirred at 18 for 15 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition) to give Product **54** (10 mg, 22.76 μ mol, 20.46% yield) as a white solid. LCMS (ESI): m/z : [M + H] calcd for C₂₁H₂₁N₃O₃F₄: 439; found 440; RT=2.383 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.40 - 1.52 (m, 3 H) 1.57 (br d, $J=6.53$ Hz, 3 H) 1.63 - 1.76 (m, 2 H) 2.78 (dd, $J=13.61$, 10.60 Hz, 1 H) 3.13 (dd, $J=13.61$, 4.33 Hz, 1 H) 4.65 - 4.74 (m, 1 H) 5.22 (s, 2 H) 6.71 (s, 1 H) 6.75 (d, $J=6.78$ Hz, 1 H) 7.54 - 7.70 (m, 1 H) 7.88 (br s, 3 H) 8.34 (d, $J=8.03$ Hz, 1 H).

Example 55. Preparation of *N*-(1-(2-aminopyridin-4-yl)-4-(2,6-difluorophenoxy)-3-oxobutan-2-yl)cyclopentanecarboxamide (55)

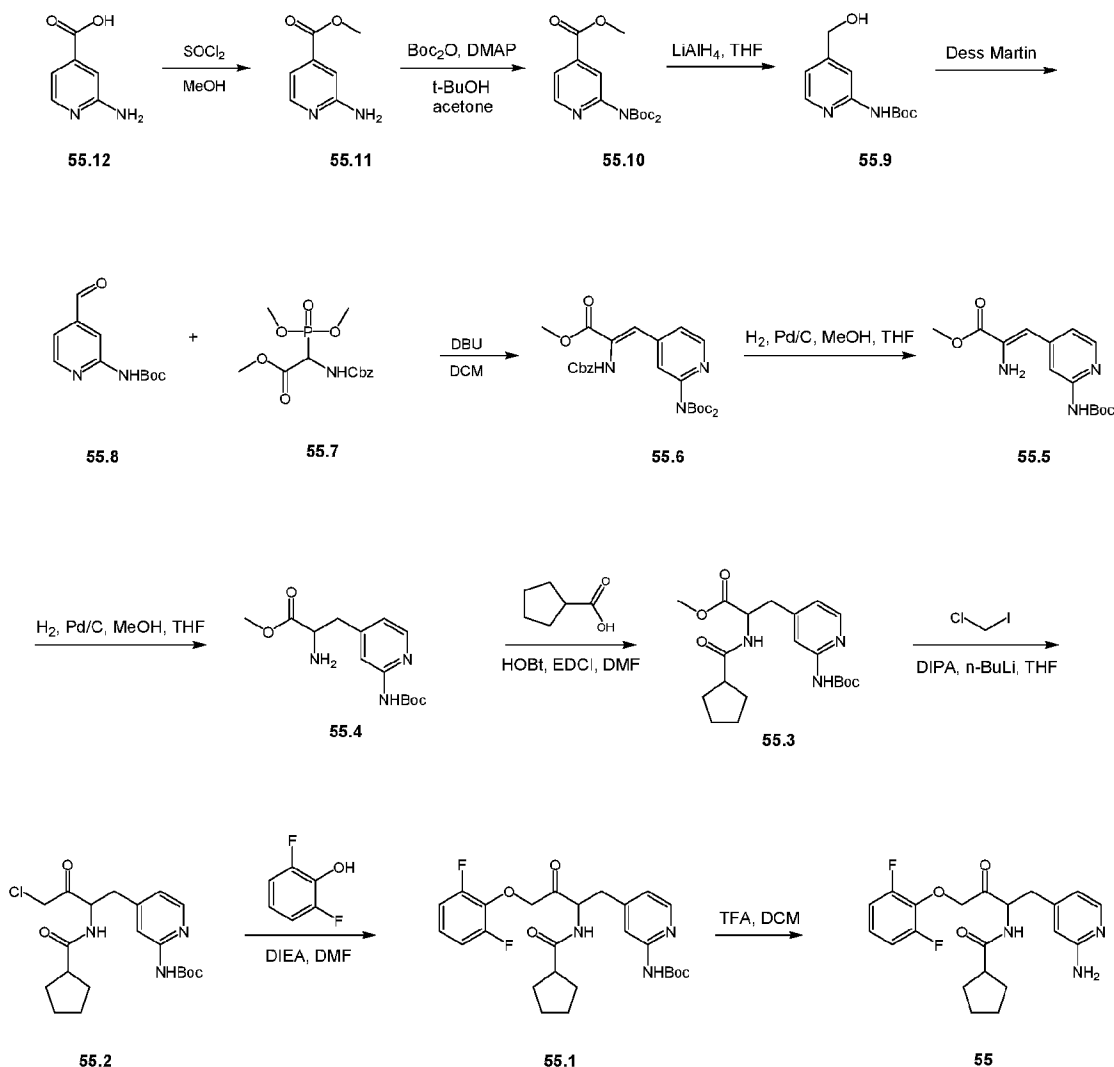
[0477] To a solution of compound **55.12** (58 g, 419.92 mmol, 1 eq) in MeOH (600 mL) was added SOCl₂ (99.92 g, 839.84 mmol, 60.93 mL, 2 eq) dropwise at 0°C under N₂. The mixture was stirred at 0 °C for 30 mins, then was heated to 18°C and stirred at 18°C for 14.5

hours. The reaction mixture was concentrated under reduced pressure to give compound **55.11** (65 g, crude) as a white solid. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{11}H_8N_2O_2$: 152; found 153; RT=0.100 min.

[0478] To a mixture of compound **55.11** (65 g, 427.21 mmol, 1 *eq*) and DMAP (2.61 g, 21.36 mmol, 0.05 *eq*) in *t*-BuOH (500 mL) and ACETONE (150 mL) was added Boc₂O (279.72 g, 1.28 mol, 294.44 mL, 3 *eq*) dropwise at 18 °C under N₂. The mixture was stirred at 18 °C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to obtain compound **55.10** (110 g, 312.16 mmol, 73.07% yield) as a white solid. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{17}H_{24}N_2O_6$: 352; found 353; RT=0.877 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.39 - 1.50 (m, 19 H) 3.97 (s, 3 H) 7.77 (dd, J =5.02, 1.38 Hz, 1 H) 7.82 (s, 1 H) 8.62 (d, J =5.02 Hz, 1 H).

[0479] To a solution of compound **55.10** (60 g, 170.27 mmol, 1 *eq*) in THF (1 L) was added LiAlH₄ (12.92 g, 340.54 mmol, 2 *eq*) portionwise at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then heated to 18 °C and stirred at 18 °C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H₂O 1000 mL and extracted with EtOAc 1500 mL (500 mL x 3). The combined organic layers were washed with brine 1000 mL (1000 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **55.9** (15 g, 66.89 mmol, 39.28% yield) as a white solid. LCMS (ESI): m/z : $[M + H]$ calcd for $C_{11}H_{16}N_2O_3$: 293; found 294; RT=0.313 min.

[0480] To a solution of compound **55.9** (8 g, 35.67 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (18.16 g, 42.81 mmol, 13.25 mL, 1.20 *eq*) portionwise at 18 °C under N₂. The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O 60 mL and extracted with DCM 150 mL (50 mL x 3). The combined organic layers were washed with brine 100 mL (100 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **55.8** (5.10 g, 22.95 mmol, 64.33% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.59 (s, 9 H) 7.41 (dd, J =5.08, 1.32 Hz, 1 H) 8.48 (s, 1 H) 8.52 (d, J =5.15 Hz, 1 H) 8.83 (br s, 1 H).



[0481] To a solution of compound **55.7** (1.49 g, 4.50 mmol, 1 *eq*) in DCM (15 mL) was added DBU (1.03 g, 6.75 mmol, 1.02 mL, 1.50 *eq*) in one portion at 18 °C under N_2 . The mixture was stirred at 18 °C for 0.5 hour, and then to the mixture was added compound **55.8** (1 g, 4.50 mmol, 1 *eq*) in one portion at 18 °C, then was stirred at 18 °C for 0.5 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1:1) to give compound **55.6** (1.90 g, 4.44 mmol, 98.78% yield) as a white solid.

[0482] To a solution compound **55.6** (1 g, 2.34 mmol, 1 *eq*) in MeOH (50 mL) and THF (50 mL) was added Pd-C (10%, 100 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50psi) at 20 °C for 15 hours. The reaction mixture was filtered and concentrated under reduced pressure to give compound **55.5** (700 mg, crude) as a white solid. LCMS (ESI): m/z : $[\text{M} + \text{H}]$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_4$: 293; found 294; RT =0.638 min.

[0483] To a solution of compound **55.5** (600 mg, 2.05 mmol, 1 *eq*) in MeOH (50 mL) and THF (50 mL) was added Pd-C (10%, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 20°C for 15 hours. The reaction mixture was filtered and concentrated under reduced pressure to give compound **55.4** (600 mg, crude) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₁₄H₂₁N₃O₄: 295; found 296; RT=0.239 min.

[0484] To a mixture of cyclopentanecarboxylic acid (193.24 mg, 1.69 mmol, 184.04 µL, 1 *eq*) and EDCI (357.01 mg, 1.86 mmol, 1.10 *eq*) in DMF (10 mL) was added HOBt (251.64 mg, 1.86 mmol, 1.10 *eq*) in one portion at 0°C under N₂. The mixture was stirred at 0 °C for 1 hour, then the mixture was added dropwise a solution of compound **55.4** (500 mg, 1.69 mmol, 1 *eq*) in DMF(5 mL), then the mixture was added dropwise DIPEA (656.42 mg, 5.08 mmol, 887.05 µL, 3 *eq*) and stirred at 0°C for 1 hours. The reaction mixture was diluted with H₂O 10 mL and extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with brine 15 mL (15 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **55.3** (600 mg, 1.53 mmol, 90.69% yield) as a white solid. LCMS (ESI): m/z: [M + H] calcd for C₂₀H₂₉N₃O₅: 391; found 392; RT=0.681 min. ¹H NMR (400 MHz, chloroform-*d*) δ ppm 1.43 - 1.62 (m, 9 H) 1.66 - 1.93 (m, 5 H) 2.49 - 2.62 (m, 1 H) 3.02 - 3.12 (m, 1 H) 3.14 - 3.25 (m, 1 H) 3.71 - 3.87 (m, 2 H) 4.86 - 5 (m, 1 H) 5.96 (br d, *J*=7.53 Hz, 1 H) 6.72 (d, *J*=5.02 Hz, 1 H) 7.77 (s, 1 H) 8 (s, 1 H) 8.16 (d, *J*=5.02 Hz, 1 H).

[0485] To a solution of DIPA (426.51 mg, 4.21 mmol, 592.38 µL, 5.50 *eq*) in THF (10 mL) was added n-BuLi (270.01 mg, 4.21 mmol, 5.50 *eq*) at 0°C, the mixture was stirred at 0 °C for 30 mins. The mixture was added to a solution of compound **55.3** (300 mg, 766.36 µmol, 1 *eq*) and chloro(iodo)methane (675.85 mg, 3.83 mmol, 278.13 µL, 5 *eq*) in THF (10 mL) at -78°C. The mixture was stirred at -78°C for 30 mins. The reaction mixture was quenched by addition aq sat NH₄Cl 5 mL, and then extracted with EtOAc 15 mL (5 mL x 3). The combined organic layers were washed with aq sat Na₂SO₃ 10 mL (10 mL x 1), and brine 10 mL (10 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **55.2** (400 mg, crude) as a white solid.

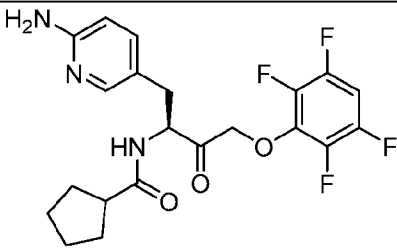
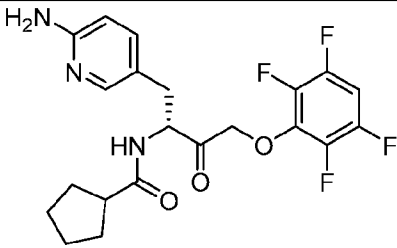
[0486] To a mixture of compound **55.2** (400 mg, 975.82 µmol, 1 *eq*) and 2,6-difluorophenol (126.95 mg, 975.82 µmol, 1 *eq*) in DMF (5 mL) was added DIEA (504.46

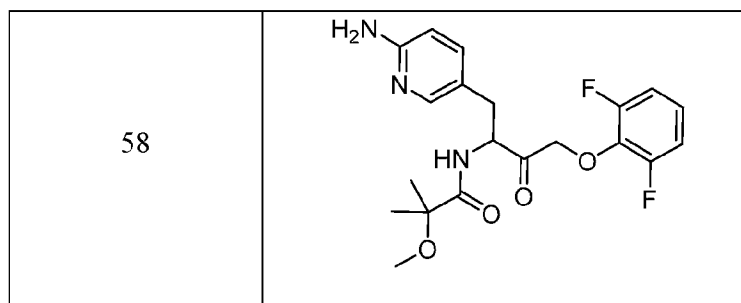
mg, 3.90 mmol, 681.70 μ L, 4 *eq*) in one portion at 20°C under N₂. The mixture was stirred at 20 °C for 10 hours. The residue was purified by prep-HPLC (neutral condition) to give compound **55.1** (60 mg, 119.16 μ mol, 12.21% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₂₆H₃₁N₃O₅F₂: 503; found 504; RT=0.804 min.

- 5 **[0487]** To a solution of compound **55.1** (60 mg, 119.16 μ mol, 1 *eq*) in DCM (3 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL, 113.35 *eq*) in one portion at 18°C under N₂. The mixture was stirred at 18°C for 15 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition) and SFC (condition: neutral condition) to give product **55** (10 mg, 24.79 μ mol, 25% yield) as a white solid. LCMS (ESI): *m/z*: [M + H] calcd for C₂₁H₂₃N₃O₃F₂: 403; found 404; RT=2.518 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 1.46 - 1.58 (m, 3 H) 1.58 - 1.71 (m, 3 H) 1.71 - 1.85 (m, 2 H) 2.56 - 2.65 (m, 1 H) 2.71 - 2.80 (m, 1 H) 3.14 (dd, *J*=14, 5.40 Hz, 1 H) 4.85 - 5.02 (m, 2 H) 6.41 - 6.55 (m, 2 H) 6.93 - 7.03 (m, 2 H) 7.03 - 7.11 (m, 1 H) 7.69 - 7.79 (m, 1 H).

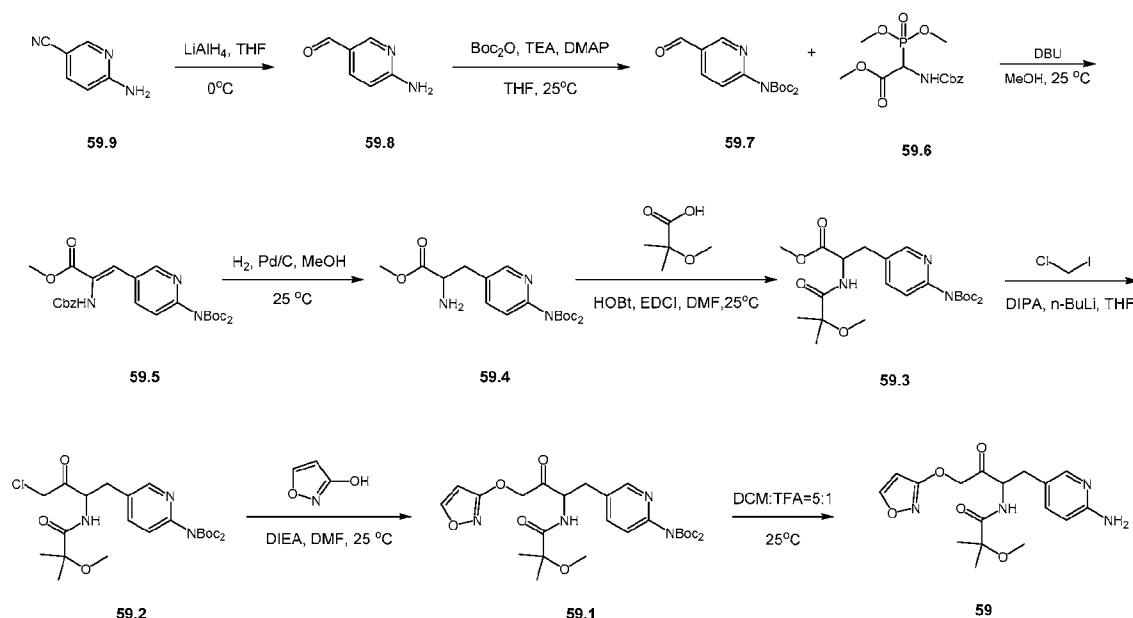
- 15 **Examples 56, 57, and 58.** (*S*)-*N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)cyclopentanecarboxamide (**56**); (*R*)-*N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)cyclopentanecarboxamide (**57**); and *N*-(1-(6-aminopyridin-3-yl)-4-(2,6-difluorophenoxy)-3-oxobutan-2-yl)-2-methoxy-2-methylpropanamide (**58**)

- 20 **[0488]** Compounds 56, 57, and 58 were prepared according to the methods described above.

Compound No.	Structure
56	
57	



Example 59. Preparation of *N*-(1-(6-aminopyridin-3-yl)-4-(isoxazol-3-yloxy)-3-oxobutan-2-yl)-2-methoxy-2-methylpropanamide (59)



- 5 [0489] To a solution compound **59.9** (20 g, 167.89 mmol, 1 eq) in THF (500 mL) was added LiAlH₄ (12.74 g, 335.78 mmol, 2 eq) portions wise at 0 °C under N₂. The mixture was stirred at 0 °C for 2 hours. The reaction mixture was quenched by the addition of Na₂SO₄·10H₂O (30 g) then filtered. The filtrate was diluted with H₂O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500mL),
- 10 dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **59.8** (10 g, 81.88 mmol, 49% yield) as a yellow solid.

- [0490] To a mixture of compound **59.8** (10 g, 81.88 mmol, 1 eq) and TEA (33.14 g, 327.53 mmol, 4.5 eq) in THF (150 mL) was added Boc₂O (53.61 g, 245.65 mmol, 3 eq) and DMAP (1.60 g, 13.10 mmol, 0.16 eq) in one portion at 25 °C under N₂. The
- 15 mixture was stirred at 25 °C for 10 hours. The reaction mixture was quenched by addition of

Na₂SO₄·10H₂O (30g), then filtered. The filtrate was diluted with H₂O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **59.7** (11 g, 34.12 mmol, 42% yield) as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₆H₂₃N₂O₅: 323; found 323; RT=1.537min. ¹H NMR (400 MHz, chloroform-d) δ: 1.50 (s, 18 H), 7.65 (d, *J*=8.33 Hz, 1 H), 8.18(dd, *J*=8.77, 2.19 Hz, 1 H), 8.86 (d, *J*=2.19 Hz, 1 H), 10.02 - 10.10 (m, 1 H) ppm.

[0491] To a mixture of compound **59.7** (9.5 g, 29.47 mmol, 1 eq) and **59.6** (9.76 g, 29.47 mmol, 1 eq) in DCM (60 mL) was added DBU (8.97 g, 58.94 mmol, 8.88 mL, 2 eq) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction mixture was quenched by addition Na₂SO₄·10H₂O (30 g), then filtered, and then the filtrate was diluted with H₂O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **59.5** (7 g, 13.27 mmol, 45% yield) as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₇H₃₄N₃O₈: 528; found 528; RT=1.60 min.

[0492] To a solution of compound **59.5** (7 g, 13.27 mmol, 1 eq) in MeOH (200 mL) was added 10% Pd on carbon catalyst (800 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25°C for 10 hours. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **59.4** (2.8 g, 7.08 mmol, 53% yield) as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₉H₃₀N₆O₃: 396; found 396; RT=1.029 min.

[0493] To a mixture of compound **59.4** (836.43 mg, 7.08 mmol, 1 eq) and EDCI (1.63 g, 8.50 mmol, 1.2 eq) in DMF (30 mL) was added HOBt (1.15 g, 8.50mmol, 1.2 eq) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 60 min, then the mixture was added 2-methoxy-2-methylpropanoic acid (2.8 g, 7.08 mmol, 1 eq) and DIPEA (2.75 g, 21.24 mmol, 3.70 mL, 3 eq), then the mixture was stirred at 0 °C for 60 mins. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with H₂O (50 mL x 3), The combined organic layers were washed with

brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **59.3** (3 g, 6.05 mmol, 86% yield) as yellow oil. LCMS (ESI): m/z: [M + H -Boc] calcd for C₁₉H₃₀N₃O₆: 496; found 396; RT=1.516 min.

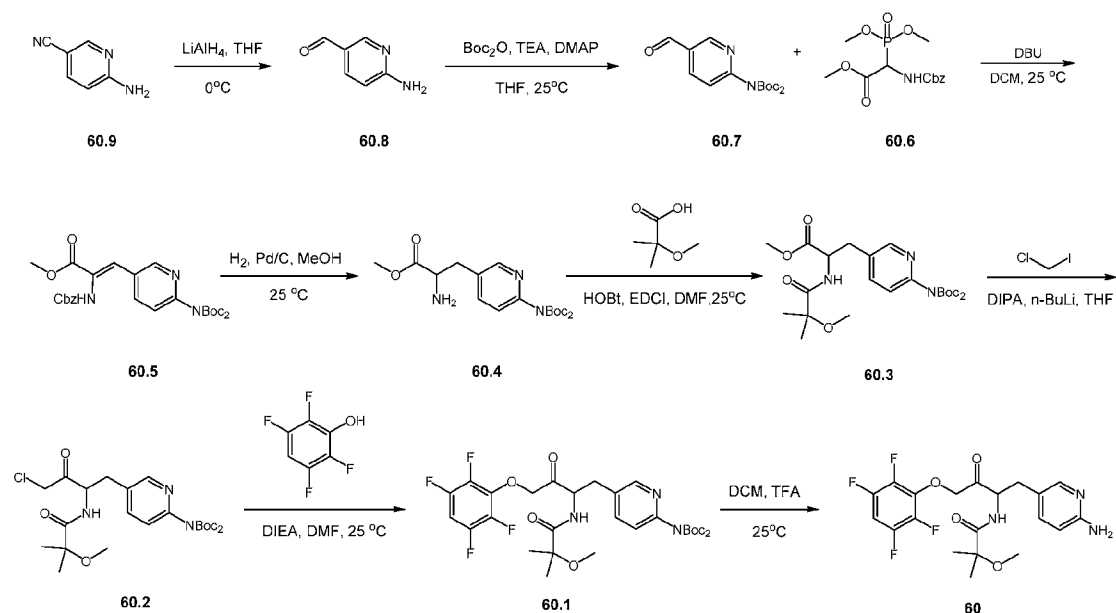
- 5 [0494] To a solution of DIPA (1.80 g, 17.76 mmol, 2.51 mL, 5.5 eq) in THF (50 mL) was added n-BuLi (2.5 M, 7.10 mL, 5.5 eq) at 0 °C, the mixture was stirred at 0 °C for 30 mins. To the mixture was added a solution of compound **59.3** (1.6 g, 3.23 mmol, 1 eq) and chloriodomethane (3.13 g, 17.76 mmol, 1.29 mL, 5.5 eq) in THF (50 mL) at -78 °C, then added DIPA (1.80 g, 17.76 mmol, 2.51 mL, 5.5 eq) at -78 °C. The mixture was stirred at -78
10 °C for 3h. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with H₂O (50 mL x 3), The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **59.2** (100 mg, 194.55 μmol, 6%
15 yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₃₇N₃O₇ Cl: 514; found 514; RT=1.414 min.

- [0495] To a mixture of compound **59.2** (100 mg, 194.55 μmol, 1 eq) and isoxazol-3-ol (16.55 mg, 194.55 μmol, 1 eq) in DMF (2 mL) was added DIPEA (75.43 mg, 583.65 μmol, 101.66 μL, 3 eq) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10
20 hours. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with H₂O (50 mL x 3); the combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **59.1** (150 mg) as a white solid.
25 LCMS (ESI) m/z: [M + H-Boc] calcd for C₂₂H₃₁N₄O₇: 563; found 463; RT= 0.937min.

- [0496] To a solution of compound **59.1** (300 mg, 533.23 μmol, 1 eq) in DCM (5 mL) was added TFA (533.23 μmol, 40 μL, 1 eq) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 30 mins. The residue was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with H₂O (50 mL x 3) then
30 washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give **59** (20mg) as a white solid. LCMS (ESI) m/z: [M

+ H]⁺ calcd for C₁₇H₂₃N₄O₅: 363; found 363; RT=2.357 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.23 (s, 3 H), 1.33 (s, 3 H), 2.84 (dd, *J*=14.55, 9.66 Hz, 1 H), 3.21 - 3.28 (m, 4 H), 4.83 - 4.83 (m, 1 H), 5.06 (d, *J*=1.22 Hz, 2 H), 6.18 (d, *J*=1.83 Hz, 1 H), 6.92 - 6.98 (m, 1 H), 7.67 (d, *J*=1.47 Hz, 1 H), 7.88 (dd, *J*=9.17, 2.08 Hz, 1 H) and 8.39 (d, *J*=1.83 Hz, 1 H) ppm.

Example 60. Preparation of *N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)-2-methoxy-2-methylpropanamide (60)



[0497] To a solution of compound **60.9** (10 g, 83.95 mmol, 1 *eq*) in THF (300 mL) was added LAH (6.37 g, 167.9 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1.5 hour. The reaction mixture was quenched by addition of saturated sodium sulfate at 0 °C and added 300 mL of H₂O then extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with saturated brine (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **60.8** (10 g, crude) as a yellow solid.

[0498] To a solution of compound **60.8** (10 g, 81.9 mmol, 1 *eq*) in THF (200 mL) was added TEA (33.14 g, 327.6 mmol, 4 *eq*), Boc₂O (53.62 g, 245.67 mmol, 56.44 mL, 3 *eq*) and DMAP (2 g, 16.38 mmol, 0.2 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O (300 mL) at 25 °C and extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with saturated brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂,

Petroleum ether/Ethyl acetate=2:1) to give compound **60.7** (4 g, 12.41 mmol, 15% yield) as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₆H₂₂N₂O₅: 323; found 167; RT=1.537 min.

[0499] To a solution of compound **60.7** (1 g, 3.1 mmol, 1 *eq*) in DCM (30 mL) was added
5 DBU (944.53 mg, 6.20 mmol, 935.18 μ L, 2 *eq*) and compound **60.6** (1.03 g, 3.1 mmol, 1 *eq*).
The mixture was stirred at 25 °C for 1 hour. The reaction mixture was quenched by addition
H₂O (100 mL) at 25 °C and extracted with ethyl acetate (100 mL x 3). The combined organic
layers were washed with saturated brines (5 mL), dried over anhydrous sodium sulfate,
filtered and concentrated under reduced pressure to give a crude product. The residue was
10 purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give
compound **60.5** (2.6 g, 4.9 mmol, 79% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺
calcd for C₂₇H₃₃N₃O₈: 528; found 528; RT=1.612 min.

[0500] To a solution of compound **60.5** (2.6 g, 4.93 mmol, 1 *eq*) in MeOH (200 mL) was
added 10% palladium on carbon (1 g) under N₂. The suspension was degassed under vacuum
15 and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 15
hours. The reaction mixture was filtered, and the filter was concentrated to give compound
60.4 (900 mg, 2.28 mmol, 46% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for
C₁₉H₂₉N₃O₆: 396; found 396; RT=1.161 min.

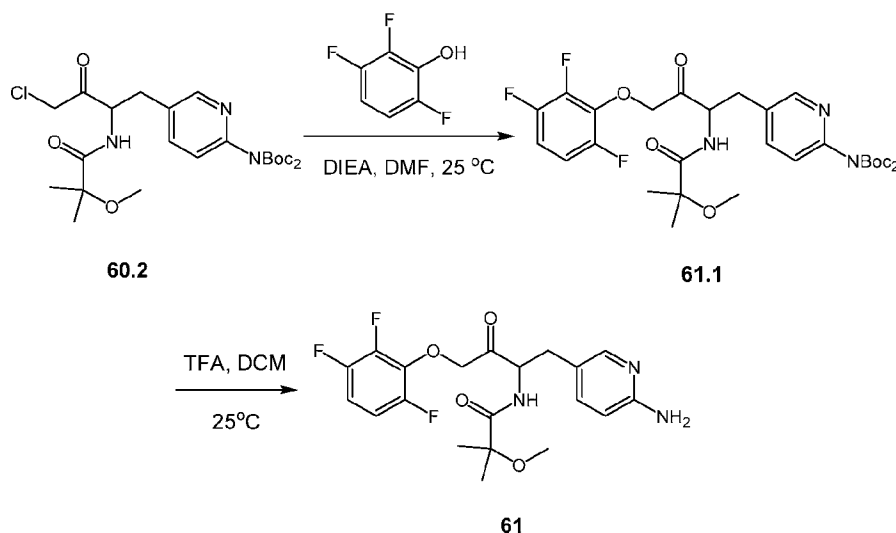
[0501] To a solution of 2-methoxy-2-methylpropanoic acid (268.85 mg, 2.28 mmol, 1 *eq*)
20 in DMF (15 mL) was added HOBt (338.3 mg, 2.5 mmol, 1.1 *eq*) and EDCI (479.9 mg, 2.5
mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 1 hr. To this mixture was added
compound **60.4** (900 mg, 2.28 mmol, 1 *eq*) and DIPEA (1.18 g, 9.1 mmol, 1.6 mL, 4 *eq*). The
mixture was stirred at 25 °C for 14 hours. The reaction mixture was quenched by addition
H₂O (30 mL) at 25 °C and extracted with ethyl acetate (30 mL x 3). The combined organic
25 layers were washed with saturated brines (5 mL), dried over anhydrous sodium sulfate,
filtered and concentrated under reduced pressure to give a crude product. The residue was
purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give
compound **60.3** (960 mg, 1.94 mmol, 85% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺
calcd for C₂₄H₃₇N₃O₈: 496; found 496; RT=1.487 min. ¹H NMR (400 MHz, chloroform-*d*) δ :
30 1.35 (d, *J*=8.38 Hz, 6 H), 1.43 (s, 19 H), 3.06 - 3.31 (m, 5 H), 3.74 (s, 3 H), 4.72 - 4.97 (m, 1
H), 7.09 - 7.21 (m, 2 H), 7.53 (dd, *J*=8.16, 2.21 Hz, 1 H) and 8.24 (d, *J*=2.20 Hz, 1 H) ppm.

[0502] To a solution of DIPA (842.3 mg, 8.32 mmol, 1.18 mL, 5.5 *eq*) in THF (5 mL) was added n-BuLi (2.5 M, 3.33 mL, 5.5 *eq*) then was stirred at 0 °C for 0.5 hr under N₂. Then to the mixture was added to the solution of compound **60.3** (750 mg, 1.51 mmol, 1 *eq*) and chloriodomethane (1.47 g, 8.32 mmol, 604.19 µL, 5.5 *eq*) in THF (15 mL) was stirred at -78 °C for 2.5 hours. The reaction mixture was quenched by addition of saturated NH₄Cl (20 mL) at 25 °C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with saturated Na₂SO₃ (10 mL) and saturated NaHCO₃ (10 mL) and saturated brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **60.2** (50 mg, 97.3 µmol, 6 % yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₃₆N₃O₇Cl: 514; found 414; RT=1.253 min.

[0503] To a solution of compound **60.2** (40 mg, 77.8 µmol, 1 *eq*) in DMF (2 mL) was added DIEA (30.17 mg, 233.5 µmol, 40.7 µL, 3 *eq*) and 2,3,5,6-tetrafluorophenol (19.4 mg, 116.73 µmol, 1.5 *eq*). The mixture was stirred at 25 °C for 12 hours. The reaction mixture was quenched by addition H₂O (10) mL at 25°C and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **60.1** (20 mg, 31.07 µmol, 40% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₃₀H₃₇N₃O₈F₄: 644; found 544; RT=1.402 min.

[0504] A mixture of compound **60.1** (20 mg, 31.07 µmol, 1 *eq*) in TFA (1 mL) and DCM (5 mL) was stirred at 25 °C for 15 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition) to give **60** (10 mg, 22.55 µmol, 73% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₀H₂₁N₃O₄F₄: 444; found 444; RT=1.68 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ: 1.15 - 1.33 (m, 6 H), 2.72 - 2.90 (m, 1 H), 3.04 - 3.23 (m, 4 H), 4.94 - 5 (m, 1 H), 5.02 - 5.25 (m, 2 H), 6.53 (br d, *J*=8.16 Hz, 1 H), 7.12 (br s, 1 H), 7.37 (br d, *J*=7.50 Hz, 1 H) and 7.65 - 7.78 (m, 1 H) ppm.

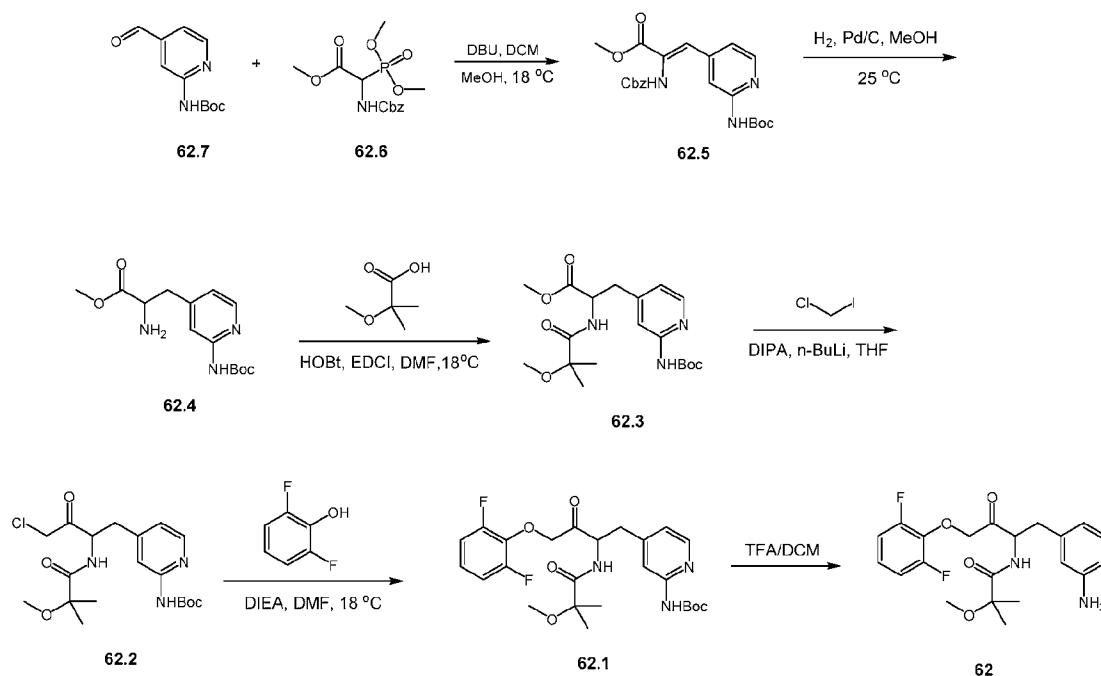
Example 61. Preparation of *N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,6-trifluorophenoxy)butan-2-yl)-2-methoxy-2-methylpropanamide (61)



[0505] To a solution of compound **60.2** (50 mg, 97.3 μmol , 1 *eq*) in DMF (3 mL) was
 5 added DIEA (37.72 mg, 291.82 μmol , 50.83 μL , 3 *eq*) and 2,3,6-trifluorophenol (28.81 mg, 194.55 μmol , 2 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition H₂O (10 mL) at 25 °C and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated brine (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The
 10 residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **61.1** (15 mg, 24 μmol , 25% yield) as yellow oil. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₃₀H₃₈N₃O₈F₈: 626; found 526; RT=1.389 min.

[0506] A mixture of compound **61.1** (40 mg, 63.94 μmol , 1 *eq*) in TFA (1 mL) and DCM (5 mL) was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to
 15 give a residue. The residue was purified by semi-preparative scale HPLC (TFA condition) to give **61** (3 mg, 7.1 μmol , 11% yield) as a yellow solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₂N₃O₄F₃: 426; found 426; RT=1.664 min. ¹H NMR (400 MHz, DMSO-*d*₆) δ : 1.10 (s, 3 H), 1.21 (s, 3 H), 2.69 - 2.79 (m, 1 H), 2.94 (br dd, *J*=14.06, 4.16 Hz, 1 H), 3.01 (s, 3 H), 4.47 - 4.65 (m, 1 H), 4.98 - 5.30 (m, 2 H), 5.70 (s, 2 H), 6.32 (d, *J*=8.31 Hz, 1 H), 7.19 (td, *J*=9.35, 6.72 Hz, 3 H), 7.71 (s, 1 H) and 8.07 (br d, *J*=8.31 Hz, 1 H) ppm.
 20

Example 62. Preparation of *N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,6-trifluorophenoxy)butan-2-yl)-2-methoxy-2-methylpropanamide (62)



[0507] To a mixture of compound **62.7** (1.4 g, 6.3 mmol, 1 *eq*) and compound **62.6** (2.09 g, 6.3 mmol, 1 *eq*) in DCM (30 mL) was added DBU (1.92 g, 12.6 mmol, 1.9 mL, 2 *eq*) in one portion at 18°C under N₂. The mixture was stirred at 18 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. This was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **62.5** (1.2 g, 2.81 mmol, 44.6% yield) as a white solid.

[0508] To a solution of compound **62.5** (1 g, 2.34 mmol, 1 *eq*) in MeOH (20 mL) was added Pd-C (10% palladium on carbon, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25°C for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **62.4** (270 mg, 914.2 μmol, 39.1% yield) as a white solid.

[0509] To a mixture of 2-methoxy-2-methylpropanoic acid (129.6 mg, 1.1 mmol, 1.2 *eq*) and EDCI (210.31 mg, 1.1 mmol, 1.2 *eq*) in DMF (5 mL) was added HOBt (148.24 mg, 1.1 mmol, 1.2 *eq*) in one portion at 18°C under N₂. The mixture was stirred at 18 °C for 30 mins, then compound **62.4** (270 mg, 914.22 μmol, 1 *eq*) and DIPEA (354.47 mg, 2.74 mmol, 477.7 μL, 3 *eq*) were added in one portion, the mixture was stirred at 18 °C for 30 mins. The

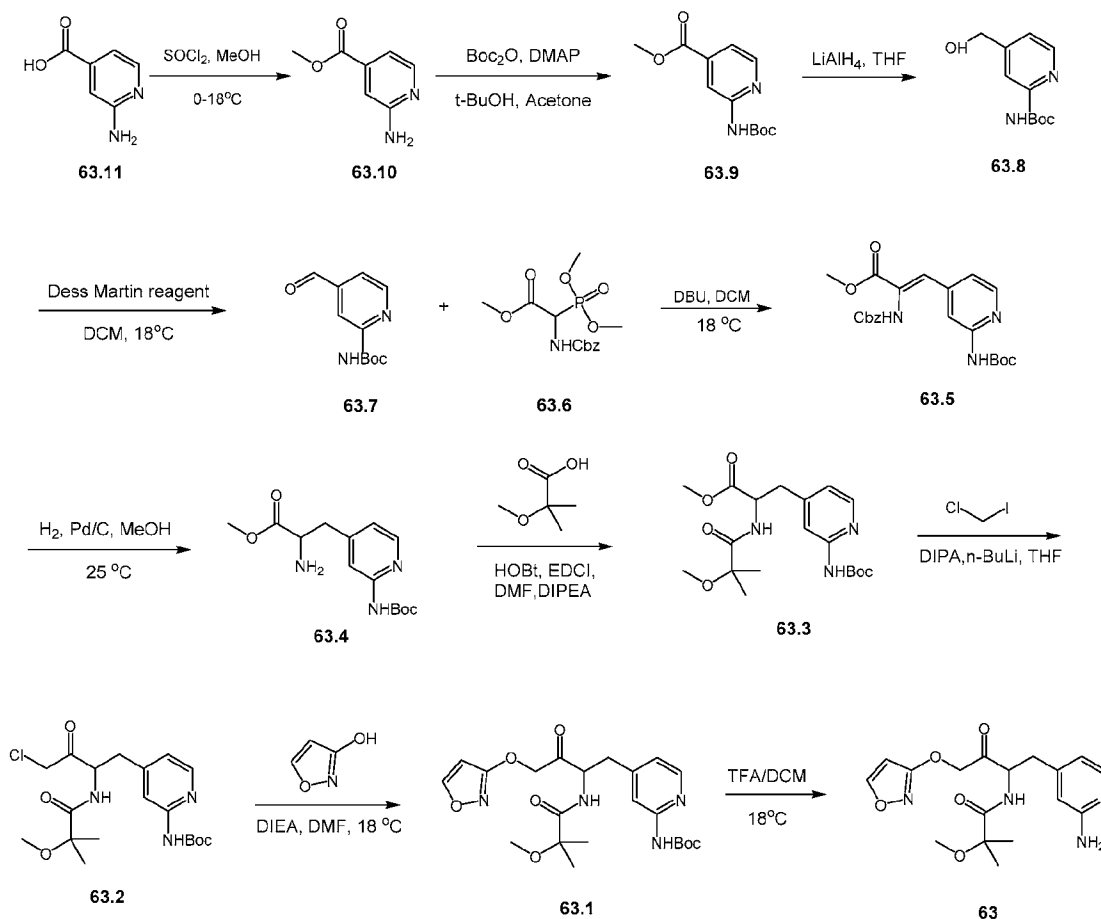
reaction mixture was diluted with H₂O (5 mL) and extracted with EtOAc (3 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. This residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **62.3** (250 mg, 632.2 μmol, 69.2% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd. for C₁₉H₂₉N₃O₆: 395; found 396; RT=0.88 min. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.12 (s, 3 H), 1.20 (s, 3 H), 1.47 (s, 9 H), 3.05 (s, 3 H), 3.06 - 3.15 (m, 2 H), 3.66 (s, 3 H), 4.49 - 4.61 (m, 1 H), 6.90 (dd, J=5.07, 1.28 Hz, 1 H), 7.71 (s, 1 H), 8.02 - 8.16 (m, 2 H) and 9.68 (s, 1 H) ppm.

[0510] To a solution of DIPA (351.8 mg, 3.5 mmol, 491.4 μL, 5.5 eq) in THF (5 mL) was added n-BuLi (2.5 M, 1.4 mL, 5.5 eq) at 0 °C, the mixture was stirred at 0 °C for 30 mins. To the mixture was added a solution of compound **62.3** (250 mg, 632.2 μmol, 1 eq) and chloriodomethane (613.3 mg, 3.48 mmol, 252.4 μL, 5.5 eq) in THF (5 mL) at -78 °C. The mixture was stirred at -78 °C for 30 minutes. The reaction mixture was quenched by addition of aqueous saturated NH₄Cl (5 mL) and extracted with EtOAc (2 mL x 3). The combined organic layers were washed with aqueous saturated Na₂SO₃ (3 mL) and brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **62.2** (400 mg, crude) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd. for C₁₉H₂₈N₃O₅Cl: 413; found 414; RT=1.2 min.

[0511] To a mixture of compound **62.2** (400 mg, 966.4 μmol, 1 eq) and 2,6-difluorophenol (125.7 mg, 966.4 μmol, 1 eq) in DMF (2 mL) was added DIEA (374.71 mg, 2.9 mmol, 505 μL, 3 eq) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The residue was purified by prep-HPLC (neutral condition) to give compound **62.1** (20 mg, 39.4 μmol, 4.1% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₅H₃₁N₃O₆F₂: 507; found 508; RT=1.076 min.

[0512] To a solution of compound **62.1** (20 mg, 39.41 μmol, 1 eq) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give **62** (8 mg, 19.6 μmol, 50 % yield) as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd. for C₂₀H₂₃N₃O₄F₂: 407; found 408; RT=2.41 min. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.11 (s, 3 H), 1.21 (s, 3 H), 2.84 - 2.94 (m, 1 H), 3.04 (s, 3 H), 3.16 - 3.24 (m, 1 H), 4.75 - 4.85 (m, 1 H), 4.97 - 5.16 (m, 2 H), 6.74 (s, 1 H), 6.79 (d, J=6.58 Hz, 1 H), 7.05 - 7.18 (m, 3 H), 7.85 (d, J=6.58 Hz, 1 H), 8.04 (br s, 2 H) and 8.35 (d, J=8.77 Hz, 1 H) ppm.

Example 63. Preparation of *N*-(1-(2-aminopyridin-4-yl)-4-(isoxazol-3-yloxy)-3-oxobutan-2-yl)-2-methoxy-2-methylpropanamide (63)



[0513] To a solution of compound **63.11** (30 g, 217.2 mmol, 1 *eq*) in MeOH (500 mL) was added SOCl_2 (103.4 g, 868.8 mmol, 63 mL, 4 *eq*) dropwise at 0 °C under N_2 , then it was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **63.10** (33 g, crude) as a white solid. LCMS (ESI): m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_9\text{N}_2\text{O}_2$: 153; found 153; RT=0.3 min.

[0514] To a mixture of compound **63.10** (10 g, 65.72 mmol, 1 *eq*) and DMAP (401.48 mg, 3.29 mmol, 0.05 *eq*) in t-BuOH (500 mL) and ACETONE (150 mL) was added Boc_2O (43 g, 197.2 mmol, 45.30 mL, 3 *eq*) dropwise at 18 °C under N_2 . The mixture was stirred at 18 °C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours then filtered to give compound **63.9** (25 g, 99.1 mmol, 50.3% yield) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ : 1.48 (s, 9 H), 3.80 - 3.96 (m, 3 H), 7.44 (dd, $J=5.07$, 1.41 Hz, 1 H), 8.33 (s, 1 H), 8.43 (d, $J=5.01$ Hz, 1 H) and 10.11 (s, 1 H) ppm.

[0515] To a solution of compound **63.9** (25 g, 99.1 mmol, 1 *eq*) in THF (500 mL) was added LiAlH₄ (7.52 g, 198.2 mmol, 2 *eq*) portion-wise at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then it was stirred at 18 °C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H₂O (1000 mL) and
5 extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **63.8** (7 g, 31.21 mmol, 31.5% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.47 (s, 8 H), 4.50 (d, J=5.73 Hz, 2 H), 5.40 (t, J=5.73 Hz, 1 H), 6.94 (dd, J=5.07, 0.66 Hz, 1 H), 7.81 (s, 1 H), 8.15 (d, J=5.07 Hz, 1 H) and 9.70 (br s, 1 H) ppm.
10

[0516] To a solution of compound **63.8** (7 g, 31.2 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (19.9 g, 46.8 mmol, 14.5 mL, 1.5 *eq*) portion-wise at 18 °C under N₂, then the mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O (60 mL) and extracted with DCM (50 mL x 3). The combined organic layers were
15 washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. This residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **63.7** (5.8 g, 26.1 mmol, 83.6% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.49 (s, 9 H), 7.42 (dd, J=4.96, 0.99 Hz, 1 H), 8.25 (s, 1 H), 8.50 (d, J=4.85 Hz, 1 H), 10.04 (s, 1 H) and 10.12 (s, 1 H) ppm.

[0517] To a mixture of compound **63.7** (5.8 g, 26.1 mmol, 1 *eq*) and compound **63.6** (8.65 g, 26.1 mmol, 1 *eq*) in DCM (60 mL) was added DBU (7.95 g, 52.2 mmol, 7.87 mL, 2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue, then it was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **63.5** (3
20 g, 7 mmol, 27% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₂H₂₆N₃O₆: 428; found 428; RT=1.34 min.

[0518] To a solution of compound **63.5** (3 g, 7 mmol, 1 *eq*) in MeOH (20 mL) was added Pd-C (10% palladium on carbon, 100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C
30 for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **63.4** (1.32 g, 4.47 mmol, 64% yield) as a white solid. LCMS (ESI) m/z: [M +

$[H]^+$ calcd for $C_{14}H_{22}N_3O_4$: 296; found 296; RT=0.694 min. 1H NMR (400 MHz, DMSO- d_6) δ : 1.46 (s, 9 H), 2.69 - 2.79 (m, 1 H), 2.81 - 2.91 (m, 1 H), 3.54 - 3.62 (m, 4 H), 6.85 (d, $J=4.82$ Hz, 1 H), 7.64 (s, 1 H), 8.10 (d, $J=4.82$ Hz, 1 H) and 9.71 (s, 1 H) ppm.

[0519] To a mixture of 2-methoxy-2-methylpropanoic acid (633.6 mg, 5.36 mmol, 1.2 *eq*) and EDCI (1.03 g, 5.36 mmol, 1.2 *eq*) in DMF (15 mL) was added HOBt (724.72 mg, 5.36 mmol, 1.2 *eq*) in one portion at 18 °C under N_2 . The mixture was stirred at 18 °C for 30 mins, then was added compound **63.4** (1.32 g, 4.47 mmol, 1 *eq*) and DIPEA (1.73 g, 13.41 mmol, 2.34 mL, 3 *eq*) in one portion, the mixture was stirred at 18 °C for 30 mins. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), 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/Ethyl acetate=2:1) to give compound **63.3** (1.5 g, 3.79 mmol, 85% yield) as a white solid. LCMS (ESI) m/z : $[M + H]^+$ calcd for $C_{19}H_{30}N_3O_6$: 396; found 396; RT=0.892 min. 1H NMR (400 MHz, METHANOL- d_4) δ : 1.31 (s, 3 H), 1.37 (s, 3 H), 1.56 - 1.64 (m, 9 H), 3.16 (dd, $J=13.89$, 9.26 Hz, 1 H), 3.25 (s, 3 H), 3.34 (dd, $J=13.89$, 4.85 Hz, 1 H), 3.84 (s, 3 H), 4.82 (dd, $J=9.15$, 4.96 Hz, 1 H), 6.96 (dd, $J=5.07$, 1.32 Hz, 1 H), 7.78 - 7.89 (m, 1 H) and 8.18 (d, $J=5.07$ Hz, 1 H) ppm.

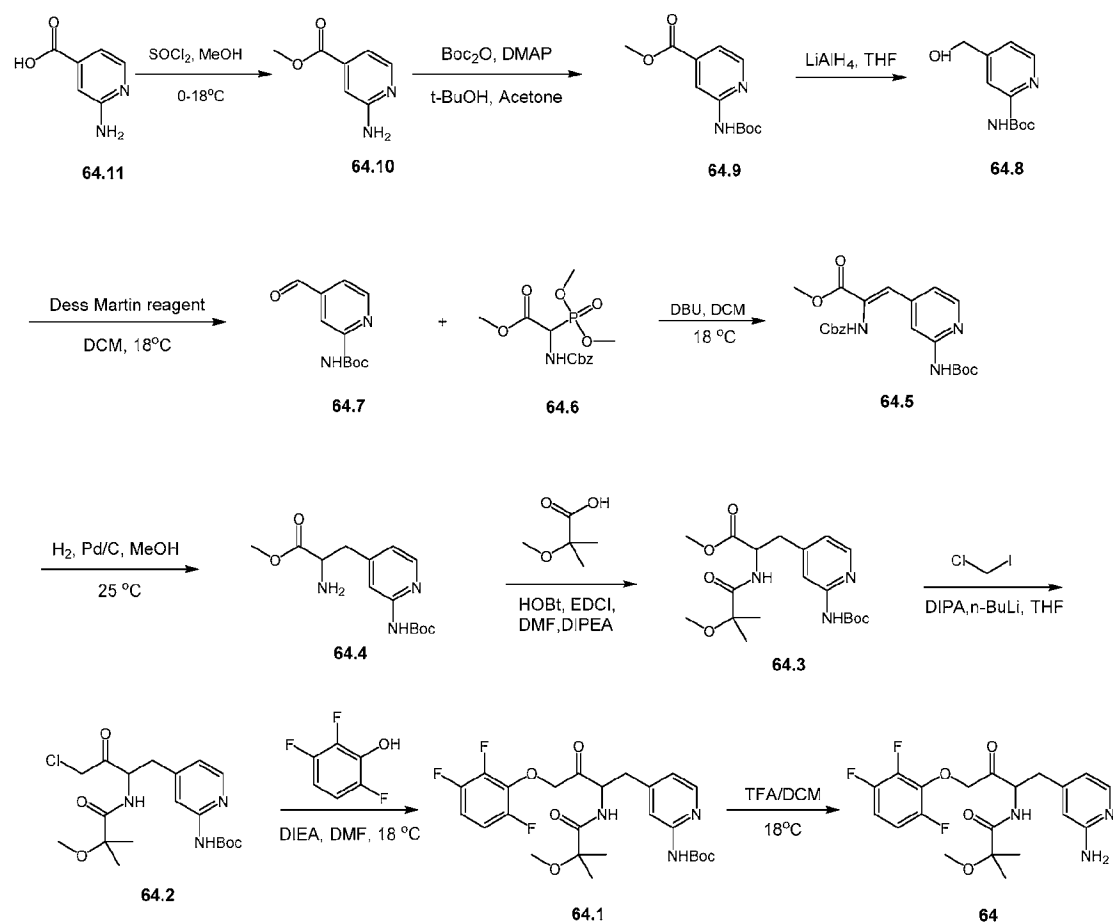
[0520] To a solution of DIPA (281.48 mg, 2.78 mmol, 393.12 μL , 5.5 *eq*) in THF (5 mL) was added *n*-BuLi (2.5 M, 1.11 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins. The mixture was added a solution of compound **63.3** (0.2 g, 505.75 μmol , 1 *eq*) and chloriodomethane (490.64 mg, 2.78 mmol, 201.9 μL , 5.5 *eq*) in THF (5 mL) at -78 °C. The mixture was stirred at -78 °C for 30 mins. The reaction mixture was quenched by addition aqueous saturated NH_4Cl (5 mL) and then extracted with EtOAc (5 mL x 3). The combined organic layers were washed with aqueous saturated Na_2SO_3 (10 mL), and brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give compound **63.2** (200 mg, crude) as yellow oil.

[0521] To a mixture of compound **63.2** (100 mg, 241.6 μmol , 1 *eq*) and isoxazol-3-ol (20.55 mg, 241.6 μmol , 1 *eq*) in DMF (2 mL) was added DIEA (93.7 mg, 724.8 μmol , 126.25 μL , 3 *eq*) in one portion at 18 °C under N_2 . The mixture was stirred at 18 °C for 10 hours. The reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (2 mL x 3). The combined organic layers were washed with brine (5 mL), 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/Ethyl acetate=1:1) to give compound **63.1** (20 mg, 43.24 μmol, 18% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₂H₃₁N₄O₇: 463; found 463; RT=1.203 min.

[0522] To a solution of compound **63.1** (20 mg, 43.24 μmol, 1 eq) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 mins. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition) to give **63** (5 mg, 13.8 μmol, 32% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₇H₂₃N₄O₅: 363; found 363; RT=2.688 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.24 (s, 3 H), 1.33 (s, 3 H), 2.96 (dd, J=14.11, 10.14 Hz, 1 H), 3.23 (s, 3 H), 3.37 (dd, J=14.11, 4.63 Hz, 1 H), 4.95 (dd, J=9.92, 4.63 Hz, 1 H), 5.06 (s, 2 H), 6.18 (d, J=1.54 Hz, 1 H), 6.82 - 6.86 (m, 2 H), 7.74 (d, J=7.06 Hz, 1 H) and 8.39 (d, J=1.76 Hz, 1 H) ppm.

Example 64. Preparation of N-(1-(2-aminopyridin-4-yl)-3-oxo-4-(2,3,6-trifluorophenoxy)butan-2-yl)-2-methoxy-2-methylpropanamide (64)



[0523] To a solution of compound **64.11** (30 g, 217.2 mmol, 1 *eq*) in MeOH (500 mL) was added SOCl₂ (103.4 g, 868.8 mmol, 63 mL, 4 *eq*) dropwise at 0 °C under N₂, then heated to 18 °C and stirred for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **64.10** (33 g, crude) as a white solid. LCMS (ESI): m/z: [M + H]⁺ calcd for C₇H₉N₂O₂: 153; found 153; RT=0.3 min.

[0524] To a mixture of compound **64.10** (10 g, 65.72 mmol, 1 *eq*) and DMAP (401.48 mg, 3.29 mmol, 0.05 *eq*) in t-BuOH (500 mL) and ACETONE (150 mL) was added Boc₂O (43.03 g, 197.17 mmol, 45.3 mL, 3 *eq*) dropwise at 18 °C under N₂. The mixture was stirred at 18 °C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to give compound **64.9** (25 g, 99.1 mmol, 50% yield) as a white solid. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.48 (s, 9 H), 3.80 - 3.96 (m, 3 H), 7.44 (dd, J=5.07, 1.41 Hz, 1 H), 8.33 (s, 1 H), 8.43 (d, J=5.01 Hz, 1 H) and 10.11 (s, 1 H) ppm.

[0525] To a solution of compound **64.9** (25 g, 99.1 mmol, 1 *eq*) in THF (500 mL) was added LiAlH₄ (7.52 g, 198.2 mmol, 2 *eq*) portion-wise at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then heated to 18 °C and stirred at 18 °C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H₂O (1000 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **64.8** (7 g, 31.21 mmol, 32% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.47 (s, 8 H), 4.50 (d, J=5.73 Hz, 2 H), 5.40 (t, J=5.73 Hz, 1 H), 6.94 (dd, J=5.07, 0.66 Hz, 1 H), 7.81 (s, 1 H), 8.15 (d, J=5.07 Hz, 1 H) and 9.70 (br s, 1 H) ppm.

[0526] To a solution of compound **64.8** (7 g, 31.21 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (19.9 g, 46.8 mmol, 14.5 mL, 1.5 *eq*) portion-wise at 18 °C under N₂. The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O (60 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **64.7** (5.8 g, 26.1 mmol, 84% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.49 (s, 9 H), 7.42 (dd, J=4.96, 0.99 Hz, 1 H), 8.25 (s, 1 H), 8.50 (d, J=4.85 Hz, 1 H), 10.04 (s, 1 H) and 10.12 (s, 1 H) ppm.

[0527] To a mixture of compound **64.7** (5.8 g, 26.1 mmol, 1 *eq*) and compound **64.6** (8.65 g, 26.1 mmol, 1 *eq*) in DCM (60 mL) was added DBU (7.95 g, 52.20 mmol, 7.87 mL, 2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified
5 by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **64.5** (3 g, 7.02 mmol, 27% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₂H₂₆N₃O₆: 428; found 428; RT=1.343 min.

[0528] To a solution of compound **64.5** (3 g, 7.02 mmol, 1 *eq*) in MeOH (20 mL) was added 10% palladium on carbon catalyst (100 mg) under N₂. The suspension was degassed
10 under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **64.4** (1.32 g, 4.47 mmol, 64% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₄H₂₂N₃O₄: 296; found 296; RT=0.694 min. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.46 (s, 9 H), 2.69 - 2.79 (m, 1 H), 2.81 - 2.91 (m, 1 H), 3.54 - 3.62 (m, 4 H),
15 6.85 (d, J=4.82 Hz, 1 H), 7.64 (s, 1 H), 8.10 (d, J=4.82 Hz, 1 H) and 9.71 (s, 1 H) ppm.

[0529] To a mixture of 2-methoxy-2-methylpropanoic acid (633.59 mg, 5.36 mmol, 1.2 *eq*) and EDCI (1.03 g, 5.36 mmol, 1.2 *eq*) in DMF (15 mL) was added HOBt (724.72 mg, 5.36 mmol, 1.2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 30 mins,
20 and then was added compound **64.4** (1.32 g, 4.47 mmol, 1 *eq*) and DIPEA (1.73 g, 13.41 mmol, 2.34 mL, 3 *eq*) in one portion, the mixture was stirred at 18 °C for 30 mins. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column
25 chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **64.3** (1.5 g, 3.8 mmol, 85% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₉H₃₀N₃O₆: 396; found 396; RT=0.892 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.31 (s, 3 H), 1.37 (s, 3 H), 1.56 - 1.64 (m, 9 H), 3.16 (dd, J=13.89, 9.26 Hz, 1 H), 3.25 (s, 3 H), 3.34 (dd, J=13.89, 4.85 Hz, 1 H), 3.84 (s, 3 H), 4.82 (dd, J=9.15, 4.96 Hz, 1 H), 6.96 (dd, J=5.07, 1.32 Hz, 1 H),
30 7.78 - 7.89 (m, 1 H) and 8.18 (d, J=5.07 Hz, 1 H) ppm.

[0530] To a solution of DIPA (1.41 g, 13.91 mmol, 1.97 mL, 5.5 *eq*) in THF (20 mL) was added n-BuLi (2.5 M, 5.56 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins.

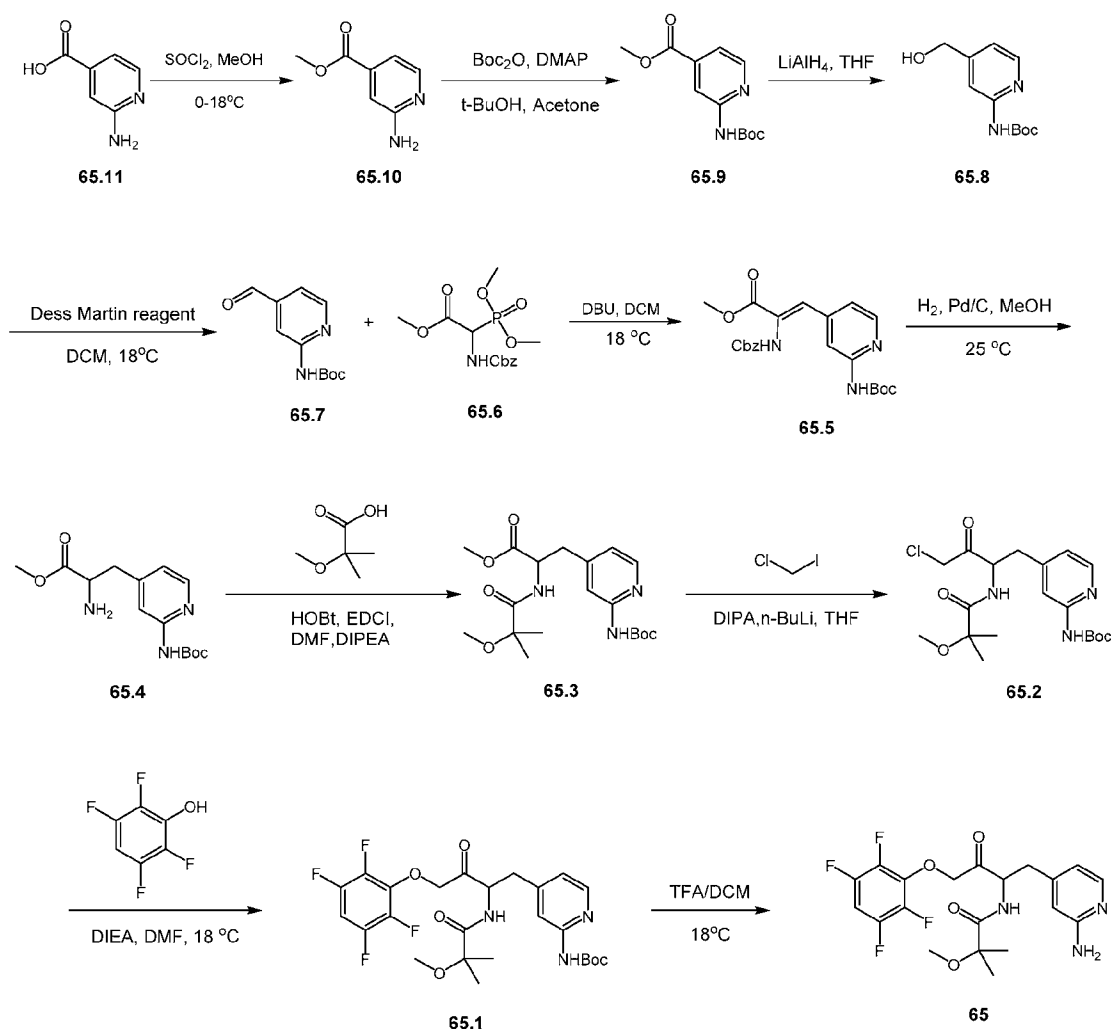
The mixture was added a solution of compound **64.3** (1 g, 2.53 mmol, 1 *eq*) and chloriodomethane (2.45 g, 13.91 mmol, 1.01 mL, 5.5 *eq*) in THF (20 mL) at -78 °C. The mixture was stirred at -78 °C for 30 mins. The reaction mixture was quenched by addition aqueous saturated NH₄Cl (20 mL) and then extracted with EtOAc (20 mL x 3). The combined
5 organic layers were washed with aqueous saturated Na₂SO₃ (30 mL), and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **64.2** (2 g) as yellow oil.

[0531] To a mixture of compound **64.2** (650 mg, 1.57 mmol, 1 *eq*) and 2,3,6-trifluorophenol (232.49 mg, 1.57 mmol, 1 *eq*) in DMF (2 mL) was added DIEA (608.89 mg, 4.71 mmol, 820.61 µL, 3 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The residue was purified by prep-HPLC (TFA condition) to give compound **64.1** (30 mg, 57.1 µmol, 4% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₅H₃₁N₃O₆F₃: 526; found 526; RT=1.353 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.22 (s, 3 H), 1.31 (s, 2 H), 1.56 - 1.61 (m, 9 H), 3.06 (dd, J=14.11, 9.92 Hz, 1 H), 3.20 (s, 2
15 H), 3.43 - 3.53 (m, 1 H), 5 - 5.13 (m, 2 H), 6.94 - 7.07 (m, 3 H), 7.21 - 7.33 (m, 2 H) and 8.11 - 8.20 (m, 1 H) ppm.

[0532] To a solution of compound **64.1** (30 mg, 57.1 µmol, 1 *eq*) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 mins. The residue was purified by prep-HPLC (TFA condition) to give **64** (10 mg, 23.51
20 µmol, 41% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₀H₂₃N₃O₄F₃: 426; found 426; RT=2.646 min. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.15 (s, 3 H), 1.22 (s, 3 H), 2.91 (dd, J=14, 10.03 Hz, 1 H), 3.07 (s, 3 H), 3.19 (dd, J=14, 4.30 Hz, 1 H), 4.77 (td, J=9.32, 4.52 Hz, 1 H), 5.09 (q, J=17.35 Hz, 2 H), 6.71 (br d, J=4.19 Hz, 2 H), 7.08 - 7.16 (m, 2 H), 7.78 - 7.82 (m, 1 H) and 8.07 (br d, J=8.82 Hz, 1 H) ppm.

25 **Example 65. Preparation of *N*-(1-(2-aminopyridin-4-yl)-3-oxo-4-(2,3,5,6-tetrafluorophenoxy)butan-2-yl)-2-methoxy-2-methylpropanamide (65)**

[0533] To a solution of compound **65.11** (30 g, 217.2 mmol, 1 *eq*) in MeOH (500 mL) was added SOCl₂ (103.36 g, 868.8 mmol, 63.02 mL, 4 *eq*) dropwise at 0 °C under N₂, then heated to 18 °C and stirred for 10 hours. The reaction mixture was concentrated under reduced
30 pressure to give compound **65.10** (33 g, crude) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₇H₉N₂O₂: 153; found 153; RT=0.298 min.



[0534] To a mixture of compound **65.10** (10 g, 65.7 mmol, 1 *eq*) and DMAP (401.5 mg, 3.29 mmol, 0.05 *eq*) in $t\text{-BuOH}$ (500 mL) and ACETONE (150 mL) was added Boc_2O (43.03 g, 197.17 mmol, 45.3 mL, 3 *eq*) dropwise at 18°C under N_2 . The mixture was stirred at 18°C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to give compound **65.9** (25 g, 99.1 mmol, 50% yield) as a white solid. ^1H NMR (400 MHz, METHANOL- d_4) δ : 1.48 (s, 9 H), 3.80 - 3.96 (m, 3 H), 7.44 (dd, $J=5.07$, 1.41 Hz, 1 H), 8.33 (s, 1 H), 8.43 (d, $J=5.01$ Hz, 1 H) and 10.11 (s, 1 H) ppm.

[0535] To a solution of compound **65.9** (25 g, 99.1 mmol, 1 *eq*) in THF (500 mL) was added LiAlH_4 (7.52 g, 198.2 mmol, 2 *eq*) portion-wise at 0°C under N_2 . The mixture was stirred at 0°C for 1 hour, then heated to 18°C and stirred at 18°C for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15 mL), filtered and then diluted with H_2O (1000 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (1000 mL), 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/Ethyl acetate=2:1) to give compound **65.8** (7 g, 31.2 mmol, 32% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.47 (s, 8 H), 4.50 (d, J=5.73 Hz, 2 H), 5.40 (t, J=5.73 Hz, 1 H), 6.94 (dd, J=5.07, 0.66 Hz, 1 H), 7.81 (s, 1 H), 8.15 (d, J=5.07 Hz, 1 H) and 9.70 (br s, 1 H) ppm.

[0536] To a solution of compound **65.8** (7 g, 31.21 mmol, 1 *eq*) in DCM (60 mL) was added Dess-Martin periodinane (19.86 g, 46.82 mmol, 14.50 mL, 1.5 *eq*) portion-wise at 18 °C under N₂. The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O (60 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **65.7** (5.8 g, 26.1 mmol, 84% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.49 (s, 9 H), 7.42 (dd, J=4.96, 0.99 Hz, 1 H), 8.25 (s, 1 H), 8.50 (d, J=4.85 Hz, 1 H), 10.04 (s, 1 H) and 10.12 (s, 1 H) ppm.

[0537] To a mixture of compound **65.7** (5.8 g, 26.1 mmol, 1 *eq*) and compound **65.6** (8.65 g, 26.1 mmol, 1 *eq*) in DCM (60 mL) was added DBU (7.95 g, 52.2 mmol, 7.87 mL, 2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **65.5** (3 g, 7.02 mmol, 27% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₂H₂₆N₃O₆: 428; found 428; RT=1.343 min.

[0538] To a solution of compound **65.5** (3 g, 7.02 mmol, 1 *eq*) in MeOH (20 mL) was added 10% palladium on carbon catalyst (100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25°C for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **65.4** (1.32 g, 4.47 mmol, 64% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₄H₂₂N₃O₄: 296; found 296; RT=0.694 min. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.46 (s, 9 H), 2.69 - 2.79 (m, 1 H), 2.81 - 2.91 (m, 1 H), 3.54 - 3.62 (m, 4 H), 6.85 (d, J=4.82 Hz, 1 H), 7.64 (s, 1 H), 8.10 (d, J=4.82 Hz, 1 H) and 9.71 (s, 1 H) ppm.

[0539] To a mixture of 2-methoxy-2-methylpropanoic acid (633.59 mg, 5.36 mmol, 1.2 *eq*) and EDCI (1.03 g, 5.36 mmol, 1.2 *eq*) in DMF (15 mL) was added HOBT (724.7 mg, 5.36

mmol, 1.2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 30 mins, and then was added compound **65.4** (1.32 g, 4.47 mmol, 1 *eq*) and DIPEA (1.73 g, 13.41 mmol, 2.34 mL, 3 *eq*) in one portion, the mixture was stirred at 18 °C for 30 mins. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **65.3** (1.5 g, 3.79 mmol, 85% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₉H₃₀N₃O₆: 396; found 396; RT=0.892 min. ¹H NMR (400 MHz, METHANOL-d₄) δ: 1.31 (s, 3 H), 1.37 (s, 3 H), 1.56 - 1.64 (m, 9 H), 3.16 (dd, J=13.89, 9.26 Hz, 1 H), 3.25 (s, 3 H), 3.34 (dd, J=13.89, 4.85 Hz, 1 H), 3.84 (s, 3 H), 4.82 (dd, J=9.15, 4.96 Hz, 1 H), 6.96 (dd, J=5.07, 1.32 Hz, 1 H), 7.78 - 7.89 (m, 1 H) and 8.18 (d, J=5.07 Hz, 1 H) ppm.

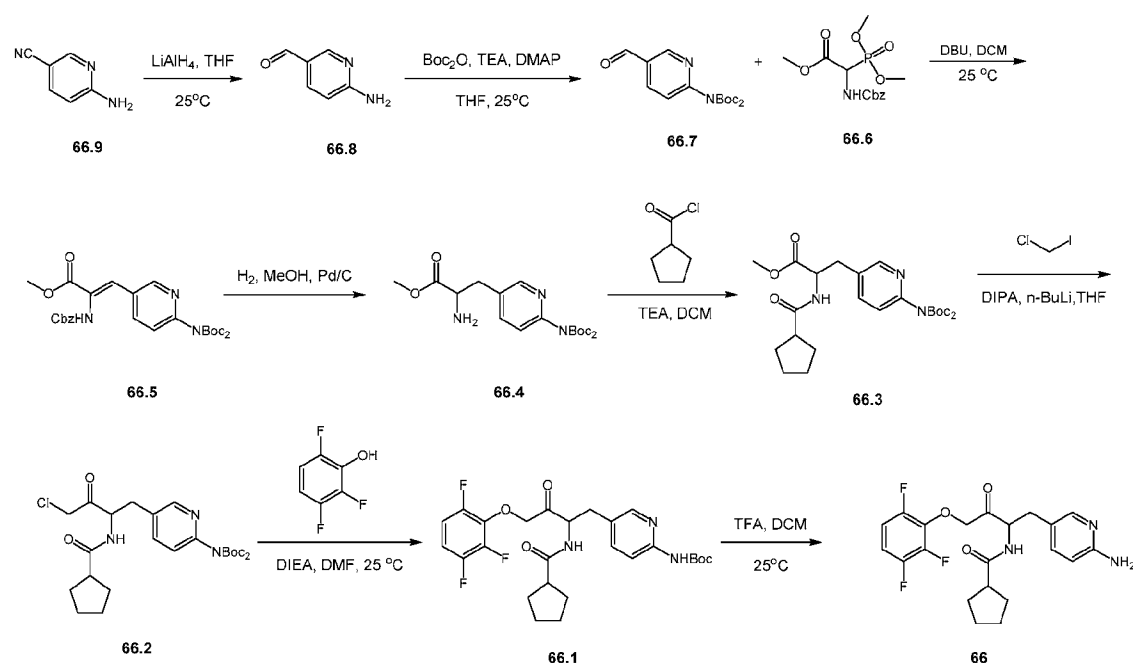
[0540] To a solution of DIPA (281.48 mg, 2.78 mmol, 393.12 μL, 5.5 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 1.11 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins. To the mixture was added a solution of compound **65.3** (200 mg, 505.75 μmol, 1 *eq*) and chloriodomethane (490.64 mg, 2.78 mmol, 201.91 μL, 5.5 *eq*) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 30 mins. The reaction mixture was quenched by addition aqueous saturated NH₄Cl (20 mL), and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with aqueous saturated Na₂SO₃ (30 mL), and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **65.2** (300 mg, crude) as yellow oil.

[0541] To a mixture of compound **65.2** (300 mg, 724.8 μmol, 1 *eq*) and 2,3,5,6-tetrafluorophenol (120.37 mg, 724.8 μmol, 1 *eq*) in DMF (2 mL) was added DIEA (281.03 mg, 2.17 mmol, 378.74 μL, 3 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was diluted with H₂O (4 mL) and extracted with EtOAc (4 mL x 3). The combined organic layers were washed with brine (5 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **65.1** (20 mg, 36.8 μmol, 5% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₅H₃₀N₃O₆F₄: 544; found 544; RT=1.366 min.

[0542] To a solution of compound **65.1** (20 mg, 36.80 μmol, 1 *eq*) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10

mins. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition) to give **65** (4 mg, 9 μ mol, 25% yield) as a white solid. LCMS (ESI) m/z : $[M + H]^+$ calcd for $C_{20}H_{22}N_3O_4F_4$: 444; found 444; $RT=2.460$ min. 1H NMR (400 MHz, METHANOL- d_4) δ : 1.02 - 1.35 (m, 6 H), 2.84 (br dd, $J=13.89, 10.58$ Hz, 1 H), 3.06 - 3.26 (m, 4 H), 4.61 (br d, $J=9.04$ Hz, 1 H), 5.04 - 5.23 (m, 2 H), 6.41 - 6.47 (m, 1 H), 6.48 - 6.55 (m, 1 H), 7.07 - 7.21 (m, 1 H) and 7.70 - 7.80 (m, 1 H) ppm.

Example 66. Preparation of *N*-(1-(6-aminopyridin-3-yl)-3-oxo-4-(2,3,6-trifluorophenoxy)butan-2-yl)cyclopentanecarboxamide (66**)**



[0543] To a solution of compound **66.9** (20 g, 167.9 mmol, 1 *eq*) in THF (250 mL) was added $LiAlH_4$ (12.74 g, 335.8 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1.5 hour. The reaction mixture was quenched by addition of saturated sodium sulfate at 0 °C and added H_2O (200 mL) then extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with saturated brines (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **66.8** (15 g, crude) as yellow oil. LCMS (ESI) m/z : $[M + H]^+$ calcd for $C_6H_7N_2O$: 123; found 123; $RT=0.21$ min.

[0544] To a solution of compound **66.8** (15 g, 122 mmol, 1 *eq*) in THF (100 mL) was added TEA (50 g, 591 mmol, 68 mL, 4 *eq*), Boc_2O (80.4 g, 368 mmol, 85 mL, 3 *eq*) and DMAP (3 g, 24.5 mmol, 0.2 *eq*). The mixture was stirred at 25 °C for 12 hours. The reaction

mixture was quenched by addition H₂O 200 mL at 25 °C and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with saturated brines (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **66.7** (8 g, 24.82 mmol, 20% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₆H₂₃N₂O₅: 323; found 323; RT=1.572 min.

[0545] To a solution of compound **66.7** (4 g, 12.4 mmol, 1 *eq*) in DCM (100 mL) was added DBU (3.8 g, 24.8 mmol, 3.8 mL, 2 *eq*) and compound **66.6** (4.1 g, 12.4 mmol, 1 *eq*). The mixture was stirred at 25 °C for 0.5 hour. The reaction mixture was quenched by addition of H₂O (100 mL) at 25 °C and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with saturated brines (5 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **66.5** (6 g, 11.37 mmol, 92% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₇H₃₄N₃O₈: 528; found 528; RT=1.613 min.

[0546] To a solution of compound **66.5** (6 g, 11.37 mmol, 1 *eq*) in MeOH (400 mL) was added 10% palladium on carbon (1 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 15 hours. The reaction mixture was filtered, and the filter was concentrated to give compound **66.4** (3.3 g, crude) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₉H₃₀N₃O₆: 396; found 396; RT=1.1445 min. ¹H NMR (400 MHz, chloroform-*d*) δ: 1.44 (s, 25 H), 2.83 - 2.97 (m, 1 H), 3.07 (dd, *J*=13.89, 5.51 Hz, 1 H), 3.68 - 3.78 (m, 4 H), 7.18 (d, *J*=8.16 Hz, 1 H), 7.60 (dd, *J*=8.16, 2.20 Hz, 1 H) and 8.32 (d, *J*=1.98 Hz, 1 H) ppm.

[0547] To a solution of compound **66.4** (2 g, 5.06 mmol, 1 *eq*) in DCM (30 mL) was added TEA (1.02 g, 10.12 mmol, 1.4 mL, 2 *eq*) and cyclopentane carbonyl chloride (804.68 mg, 6.07 mmol, 738.24 μL, 1.20 *eq*). The mixture was stirred at 25 °C for 5 min. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **66.3** (1.8 g, 3.66 mmol, 72% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₅H₃₈N₃O₇: 492; found 492; RT=1.552 min.

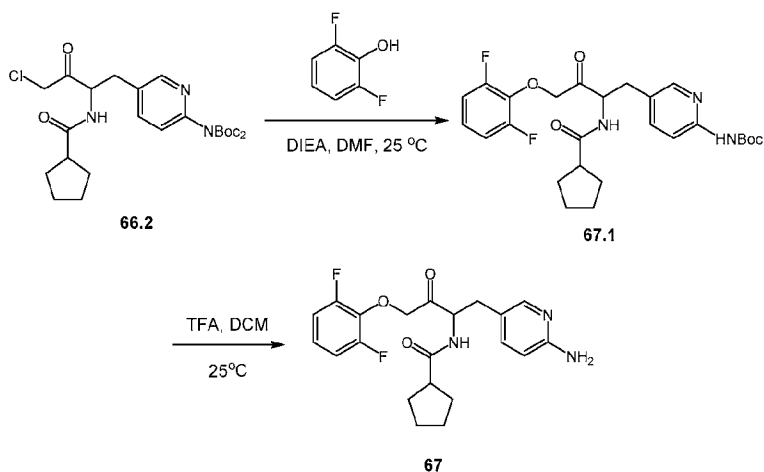
[0548] To a solution of DIPA (1.03 g, 10.17 mmol, 1.43 mL, 5 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 4.07 mL, 5 *eq*). The mixture was stirred at 0 °C for 0.5 hr under N₂.

Then the mixture was added to the solution of compound **66.3** (1 g, 2.03 mmol, 1 *eq*) and chloriodomethane (1.79 g, 10.17 mmol, 738.3 μ L, 5 *eq*) in THF (10 mL) was stirred at -78 °C for 2.5 hours. The reaction mixture was quenched by addition saturated NH₄Cl (20 mL) at 25 °C and extracted with ethyl acetate (15 mL x 3). The combined organic layers were
5 washed with saturated Na₂SO₃ (10 mL) and saturated NaHCO₃ (10 mL) and saturated brines (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound **66.2** (1.6 g) as yellow oil.

[0549] To a solution of compound **66.2** (500 mg, 1.22 mmol, 1 *eq*) in DMF (5 mL) was added DIEA (472.93 mg, 3.66 mmol, 637.37 μ L, 3 *eq*) and 2,3,6-trifluorophenol (271 mg,
10 1.83 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition saturated NaHCO₃ 20 mL at 25 °C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl
15 acetate=1:1) to give compound **66.1** (30 mg, 57.52 μ mol, 5% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₆H₃₁N₃O₅F₃: 522; found 522; RT=1.175 min.

[0550] To a solution of compound **66.1** (30 mg, 57.52 μ mol, 1 *eq*) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition saturated NaHCO₃ (20 mL) at 25 °C and extracted with ethyl acetate
20 (20 mL x 3). The combined organic layers were washed with saturated brines (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (TFA condition) to give **66** (4 mg, 9.5 μ mol, 17% yield) was obtained as a yellow solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₁H₂₃N₃O₃F₃: 422; found 422; RT=1.472 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ :
25 1.41 - 1.90 (m, 8 H), 2.63 (quin, *J*=7.66 Hz, 1 H), 2.77 (dd, *J*=14.33, 9.70 Hz, 1 H), 3.11 - 3.24 (m, 1 H), 4.86 (br s, 1 H), 4.97 - 5.14 (m, 2 H), 6.87 - 7.06 (m, 3 H), 7.66 (s, 1 H) and 7.85 (dd, *J*=9.15, 1.87 Hz, 1 H) ppm.

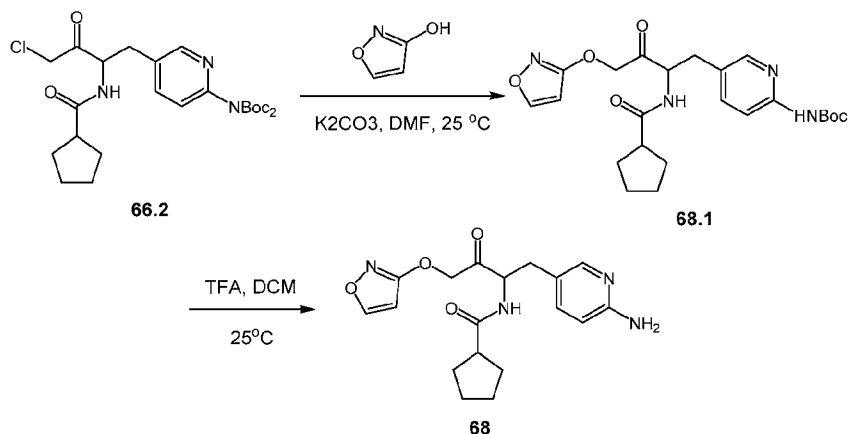
Example 67. Preparation of *N*-(1-(6-aminopyridin-3-yl)-4-(2,6-difluorophenoxy)-3-oxobutan-2-yl)cyclopentanecarboxamide (67)



[0551] To a solution of compound **66.2** (500 mg, 1.22 mmol, 1 *eq*) in DMF (5 mL) was added DIEA (472.93 mg, 3.66 mmol, 637.37 μ L, 3 *eq*) and 2,6-difluorophenol (238.07 mg, 1.83 mmol, 1.5 *eq*). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition of saturated NaHCO₃ (20 mL) at 25 °C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **67.1** (30 mg, 59.6 μ mol, 5% yield) as yellow oil. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₆H₃₂N₃O₅F₂: 504; found 504; RT=1.112 min.

[0552] To a solution of compound **67.1** (30 mg, 59.58 μ mol, 1 *eq*) in DCM (5 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by addition saturated NaHCO₃ (20 mL) at 25 °C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated brines (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by prep-HPLC (TFA condition) to give **67** (4 mg, 9.92 μ mol, 17% yield) as a yellow solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₂₁H₂₄N₃O₃F₂: 404; found 404; RT=1.422 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 1.42 - 1.94 (m, 8 H), 2.52 - 2.69 (m, 1 H), 2.76 (dd, *J*=14.44, 9.81 Hz, 1 H), 3.09 - 3.25 (m, 1 H), 4.90 - 5.04 (m, 3 H), 6.87 - 7.13 (m, 4 H), 7.65 (s, 1 H) and 7.85 (dd, *J*=9.26, 1.98 Hz, 1 H) ppm.

Example 68. Preparation of *N*-(1-(6-aminopyridin-3-yl)-4-(isoxazol-3-yloxy)-3-oxobutan-2-yl)cyclopentanecarboxamide (68)

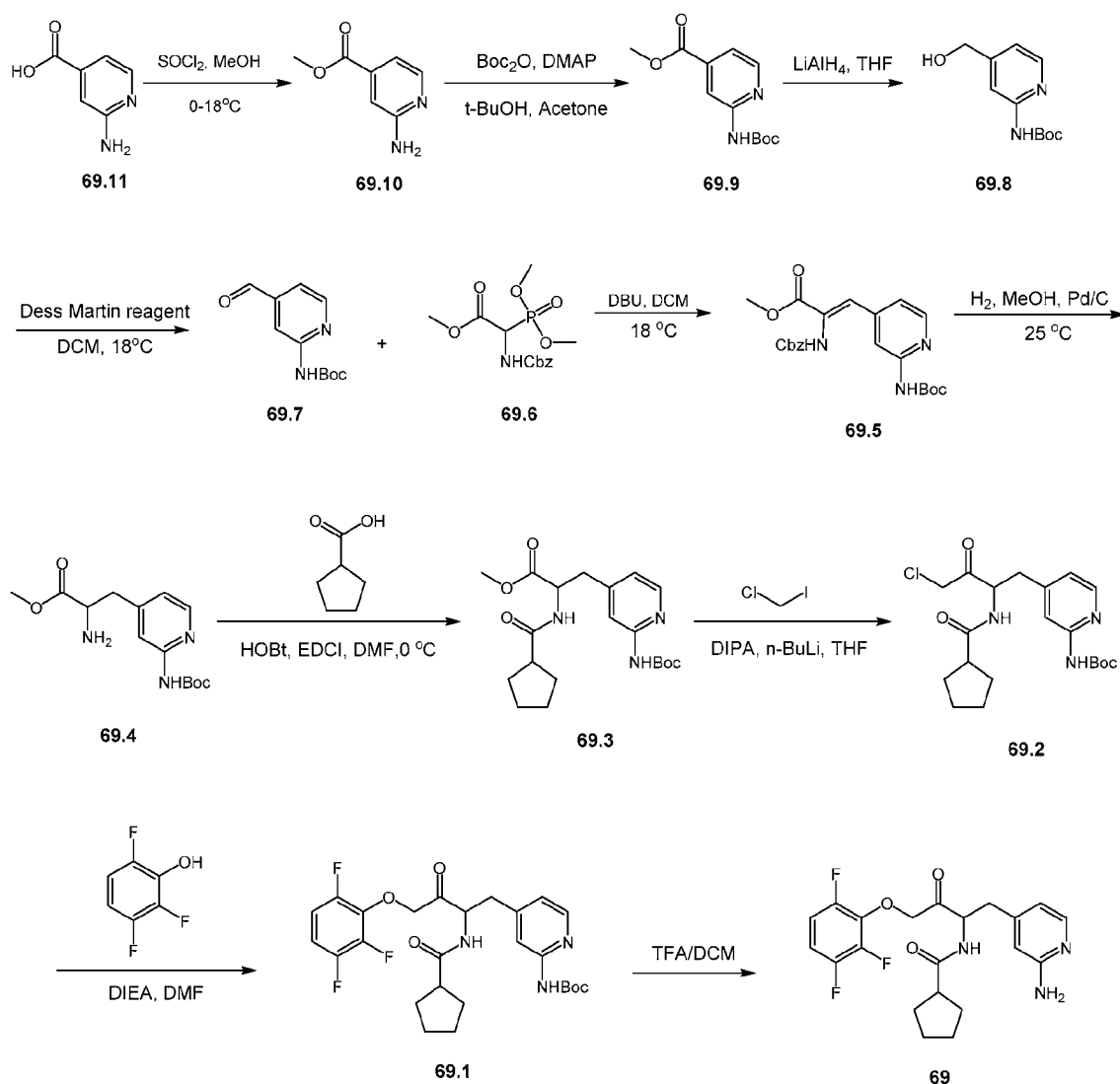


[0553] To a solution of compound **66.2** (400 mg, 975.83 μmol , 1 *eq*) in DMF (5 mL) was
 5 added K_2CO_3 (404.6 mg, 2.93 mmol, 3 *eq*) and isoxazol-3-ol (124.51 mg, 1.46 mmol, 1.5 *eq*).
 The mixture was stirred at 25 °C for 15 hours. The reaction mixture was quenched by
 addition saturated NaHCO_3 20 mL at 25°C and extracted with ethyl acetate (20 mL x 3). The
 combined organic layers were washed with saturated brines (10 mL), dried over anhydrous
 sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The
 10 residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=1:1) to
 give compound **68.1** (50 mg) as yellow oil.

[0554] A mixture of compound **68.1** (100 mg, 65.43 μmol , 1 *eq*) in TFA (1 mL) and DCM
 (5 mL) was stirred at 25 °C for 12 hours. The mixture was concentrated in vacuum. The
 residue was purified by preparative scale-HPLC (TFA condition) to give **68** (2 mg, 5.58
 15 μmol , 9% yield) as a white solid. LCMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{23}\text{N}_4\text{O}_4$: 359;
 found 359; RT=1.169 min. ^1H NMR (400 MHz, METHANOL- d_4) δ : 1.43 - 1.91 (m, 10 H),
 2.56 - 2.72 (m, 1 H), 2.79 (dd, $J=14.44$, 9.37 Hz, 1 H), 3.09 - 3.23 (m, 1 H), 4.81 (dd, $J=9.37$,
 5.40 Hz, 1 H), 5.05 (d, $J=2.43$ Hz, 2 H), 6.17 (d, $J=1.76$ Hz, 1 H), 6.93 (d, $J=9.04$ Hz, 1 H),
 7.67 (s, 1 H), 7.84 (dd, $J=9.15$, 1.87 Hz, 1 H) and 8.39 (d, $J=1.76$ Hz, 1 H) ppm.

Example 69. Preparation of *N*-(1-(2-aminopyridin-4-yl)-3-oxo-4-(2,3,6-trifluorophenoxy)butan-2-yl)cyclopentanecarboxamide (69)

[0555] To a solution of compound **69.11** (50 g, 362 mmol, 1 *eq*) in MeOH (600 mL) was
 added SOCl_2 (172.27 g, 1.45 mol, 105.04 mL, 4 *eq*) dropwise at 0 °C under N_2 , then heated
 to 18 °C and stirred for 10 hours. The reaction mixture was concentrated under reduced



pressure to give compound **69.10** (60 g, crude) as a white solid. LCMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_7\text{H}_8\text{N}_2\text{O}_2$: 152; found 153; $\text{RT}=0.214$ min.

- [0556] To a mixture of compound **69.10** (60 g, 394.35 mmol, 1 *eq*) and DMAP (2.41 g, 19.72 mmol, 0.05 *eq*) in $t\text{-BuOH}$ (600 mL) and ACETONE (200 mL) was added Boc_2O (344.26 g, 1.58 mol, 362.38 mL, 4 *eq*) dropwise at 18°C under N_2 . The mixture was stirred at 18°C for 15 hours. The solution was diluted with pentane (200 mL), cooled in the refrigerator for 3 hours and filtered to obtain compound **69.9** (42 g, 166.5 mmol, 42% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 1.38 - 1.54 (m, 9 H), 3.82 - 3.96 (m, 3 H), 7.44 (dd, $J=5.07, 1.41$ Hz, 1 H), 8.32 (s, 1 H), 8.42 (d, $J=5.14$ Hz, 1 H) and 10.11 (s, 1 H) ppm.

[0557] To a solution of compound **69.9** (42 g, 166.5 mmol, 1 *eq*) in THF (800 mL) was added LiAlH₄ (12.64 g, 333 mmol, 2 *eq*) portion-wise at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then heated to 18 °C and stirred at 18 °C for 14 hours. The reaction mixture was quenched by addition of 8% NaOH (15 mL), filtered and then diluted with H₂O (1000 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **69.8** (15 g, 67 mmol, 40% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 1.47 (s, 9 H), 4.50 (d, J=5.70 Hz, 2 H), 5.40 (t, J=5.92 Hz, 1 H), 6.89 - 6.99 (m, 1 H), 7.81 (s, 1 H), 8.14 (d, J=5.70 Hz, 1 H) and 9.71 (s, 1 H) ppm.

[0558] To a solution of compound **69.8** (15 g, 67 mmol, 1 *eq*) in DCM (150 mL) was added Dess-Martin periodinane (42.55 g, 100.33 mmol, 31.06 mL, 1.5 *eq*) portion-wise at 18 °C under N₂. The mixture was stirred at 18 °C for 2 hours. The reaction mixture was diluted with H₂O (60 mL) and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **69.7** (9 g, 40.5 mmol, 60% yield) as a white solid. ¹H NMR (400 MHz, chloroform-d) δ ppm 1.55 - 1.62 (m, 9 H), 7.40 (dd, J=5.26, 1.32 Hz, 1 H), 8.44 - 8.57 (m, 2 H), 9.38 (s, 1 H) and 10.01 - 10.11 (m, 1 H) ppm.

[0559] To a mixture of compound **69.7** (5 g, 22.5 mmol, 1 *eq*) and compound **69.6** (7.45 g, 22.5 mmol, 1 *eq*) in DCM (60 mL) was added 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (DBU) (6.85 g, 45 mmol, 6.78 mL, 2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **69.5** (5.7 g, 13.33 mmol, 59% yield) as a white solid.

[0560] To a solution of compound **69.5** (5.7 g, 13.33 mmol, 1 *eq*) in MeOH (20 mL) was added 10% palladium on carbon catalyst (100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 10 hours. The reaction mixture was filtered and concentrated under reduced

pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **69.4** (2.8 g, 9.48 mmol, 71% yield) as a white solid.

[0561] To a mixture of cyclopentanecarboxylic acid (680.21 mg, 5.96 mmol, 647.82 μ L, 1 *eq*) and EDCI (1.26 g, 6.56 mmol, 1.1 *eq*) in DMF (20 mL) was added HOBt (885.75 mg, 6.56 mmol, 1.1 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour, then the mixture was added dropwise a solution of compound **69.4** (1.76 g, 5.96 mmol, 1 *eq*) in DMF (5 mL), then the mixture was added dropwise DIPEA (2.31 g, 17.88 mmol, 3.12 mL, 3 *eq*) and stirred at 0 °C for 1 hour. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **69.3** (1.8 g, 4.6 mmol, 77% yield) as a white solid.

[0562] To a solution of DIPA (1.42 g, 14.05 mmol, 1.99 mL, 5.5 *eq*) in THF (40 mL) was added n-BuLi (2.5 M, 5.62 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins. The mixture was added a solution of compound **69.3** (1 g, 2.55 mmol, 1 *eq*) and chloriodomethane (2.48 g, 14.05 mmol, 1.02 mL, 5.5 *eq*) in THF (40 mL) at -78 °C. The mixture was stirred at -78 °C for 30 mins. The reaction mixture was quenched by addition aqueous saturated NH₄Cl (40 mL) and then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with aqueous saturated Na₂SO₃ (80 mL), and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **69.2** (1.4 g) as yellow oil.

[0563] To a mixture of compound **69.2** (300 mg, 731.87 μ mol, 1 *eq*) and 2,3,6-trifluorophenol (108.38 mg, 731.87 μ mol, 1 *eq*) in DMF (2 mL) was added DIEA (283.76 mg, 2.2 mmol, 382.43 μ L, 3 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 10 hours. The mixture was purified by semi-preparative HPLC (TFA condition) to give compound **69.1** (80 mg, 153.4 μ mol, 21% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₆H₃₀N₃O₅F₃: 522; found 522; RT=1.366 min.

[0564] To a solution of compound **69.1** (80 mg, 153.4 μ mol, 1 *eq*) in DCM (5 mL) was added TFA (1 mL) in one portion at 18 °C under N₂. The mixture was stirred at 18 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by semi-preparative HPLC (TFA condition) to give **69** (40 mg, 95 μ mol, 62% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₁H₂₃N₃O₃F₃: 442; found

5

oxobutan-2-yl)cyclopentanecarboxamide (70)

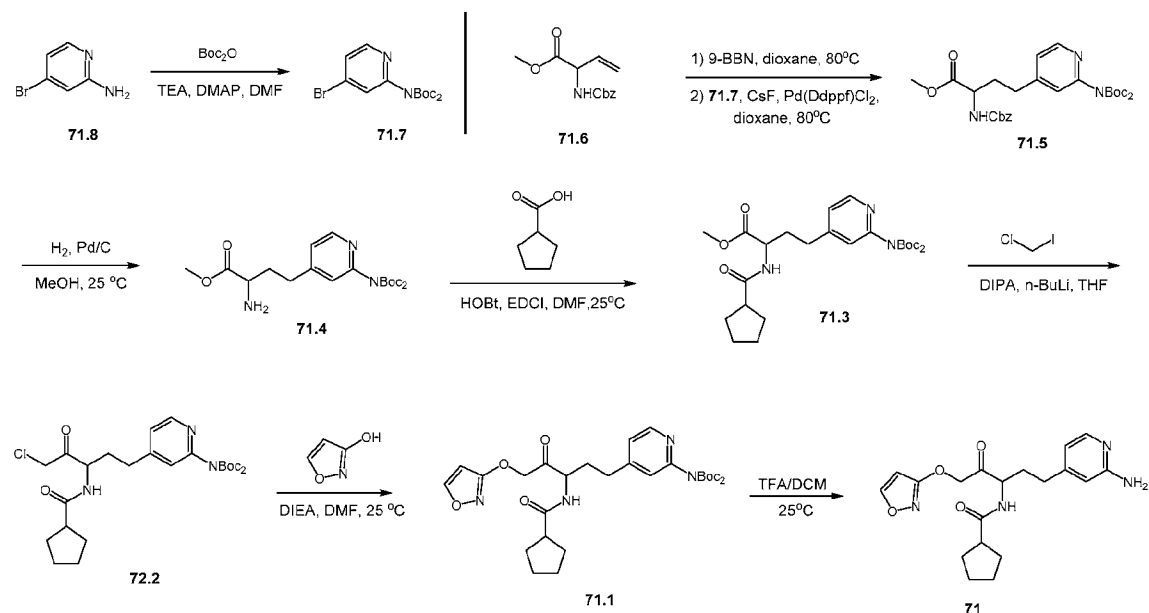


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Hz, 1 H), 6.73 (s, 1 H), 6.78 (d, J=6.61 Hz, 1 H), 7.85 (d, J=6.61 Hz, 1 H), 7.89 (br s, 1 H), 8.36 (br d, J=8.38 Hz, 1 H) and 8.68 (d, J=1.76 Hz, 1 H) ppm.

Example 71. Preparation of *N*-(5-(2-aminopyridin-4-yl)-1-(isoxazol-3-yloxy)-2-oxopentan-3-yl)cyclopentanecarboxamide (71)



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[0567] To a mixture of compound **71.8** (5 g, 28.9 mmol, 1 *eq*) and Boc₂O (25.23 g, 115.6 mmol, 26.6 mL, 4 *eq*) in DMF (50 mL) was added TEA (14.62 g, 144.5 mmol, 20.1 mL, 5 *eq*) and DMAP (353.1 mg, 2.89 mmol, 0.1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **71.7** (2.7 g, 7.23 mmol, 25% yield) as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ: 7.41 (d, J=8.93 Hz, 1 H), 8.12 (dd, J=8.56, 2.45 Hz, 1 H), 8.59 (d, J=2.20 Hz, 1 H) and 1.39 (s, 17 H) ppm.

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[0568] To a solution of compound **71.6** in dioxane (20 mL) was added 9-BBN (0.5 M, 15.9 mL, 2.2 *eq*) in one portion at 80 °C under N₂. The mixture was stirred at 80 °C for 2 hours, then to the mixture was added Pd(dppf)Cl₂ (264.20 mg, 361.07 μmol, 0.1 *eq*), CsF (1.65 g, 10.83 mmol, 399.36 μL, 3 *eq*) and compound **71.7** (1.62 g, 4.33 mmol, 1.2 *eq*). This was stirred at 80°C for 8 hours. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL),

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dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **71.5** (1 g, 1.84 mmol, 51% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₈H₃₈N₃O₈: 544; found 544; RT=1.615 min.

- 5 **[0569]** To a solution of compound **71.5** (1 g, 1.84 mmol, 1 *eq*) in MeOH (50 mL) was added 10% Pd on carbon catalyst (100 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ atmosphere (50 psi) at 25 °C for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Ethyl acetate) to give compound **71.4** (400 mg, 977 μmol, 53% yield) as a white solid. ¹H NMR (400 MHz, METHANOL-d₄) δ: 0.99 (s, 18 H), 1.44 - 1.56 (m, 1 H), 1.58 - 1.70 (m, 1 H), 2.38 (t, J=7.95 Hz, 2 H), 2.87 - 2.94 (m, 2 H), 2.89 - 2.92 (m, 1 H), 3.03 (dd, J=7.21, 5.75 Hz, 1 H), 6.86 (d, J=8.19 Hz, 1 H), 7.40 (dd, J=8.19, 2.45 Hz, 1 H) and 7.92 (d, J=2.08 Hz, 1 H) ppm.
- 10
- 15 **[0570]** To a mixture of cyclopentanecarboxylic acid (111.50 mg, 0.977 μmol, 106.2 μL, 1 *eq*) and EDCI (224.72 mg, 1.17 mmol, 1.2 *eq*) in DMF (10 mL) was added HOBt (158.39 mg, 1.17 mmol, 1.2 *eq*) in one portion at 18 °C under N₂. The mixture was stirred at 25 °C for 30 mins, then compound **71.4** (400 mg, 976.86 μmol, 1 *eq*) and DIPEA (378.76 mg, 2.93 mmol, 510.45 μL, 3 *eq*) were added in one portion. This mixture was stirred at 25 °C for 30 mins.
- 20 The reaction was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **71.3** (600 mg) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₆H₄₀O₇N₃: 506; found 506;
- 25 RT=1.316 min.

- [0571]** To a solution of DIPA (600.41 mg, 5.93 mmol, 838.6 μL, 5 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 2.37 mL, 5 *eq*) at 0 °C; the mixture was stirred at 0 °C for 30 mins. The mixture was added a solution of chloriodomethane (1.05 g, 5.93 mmol, 430.69 μL, 5 *eq*) and compound **71.3** (600 mg, 1.19 mmol, 1 *eq*) in THF (10 mL) at -78 °C. This was stirred at
- 30 -78 °C for 30 mins. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl (20 mL) and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with saturated aqueous Na₂SO₃ (30 mL), and brine (50 mL), dried over Na₂SO₄,

filtered and concentrated under reduced pressure. The residue was purified by semi-preparative scale HPLC (TFA condition) to give compound **71.2** (100 mg, 190.8 μ mol, 16% yield) as a white solid.

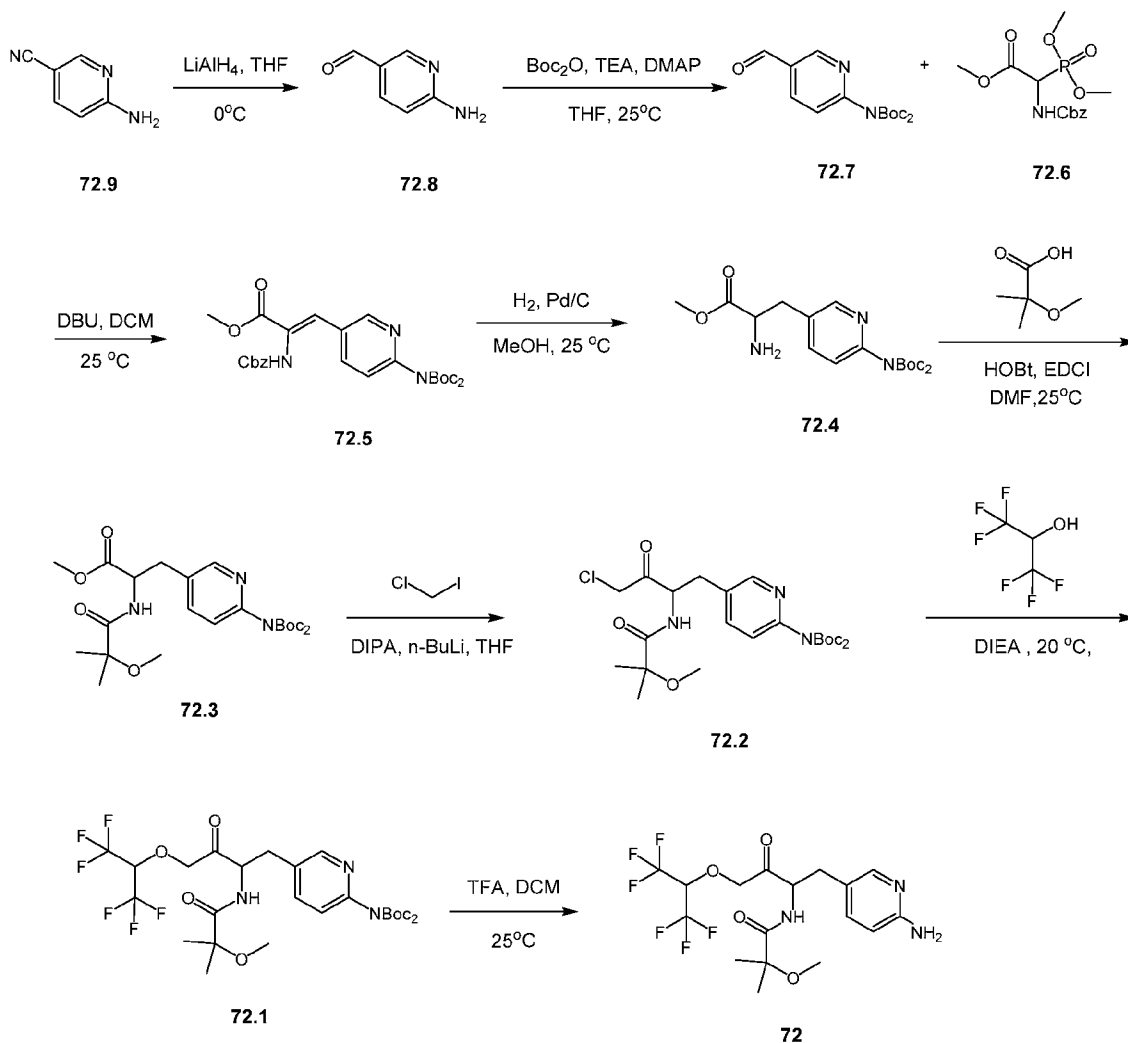
- [0572] To a mixture of compound **71.2** (70 mg, 133.6 μ mol, 1 *eq*) and isoxazol-3-ol (11.36 mg, 133.6 μ mol, 1 *eq*) in DMF (2 mL) was added DIEA (17.26 mg, 133.6 μ mol, 23.3 μ L, 1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **71.1** (80 mg) as a yellow oil.
- 10 [0573] To a solution of compound **71.1** (79.73 mg, 139.2 μ mol, 1 *eq*) in DCM (5 mL) was added TFA (139.2 μ mol, 10.31 μ L, 1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure; the residue was purified by semi-preparative scale HPLC (neutral condition) to give **71** (2 mg, 5.13 μ mol, 4% yield, 95.5% purity) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₉H₂₄N₄O₄: 373; found 373; RT=5.70 min. ¹H NMR (400 MHz, METHANOL-d₄) δ : 1.72 (m, 2 H), 1.74 (m, 4 H), 1.87 (m, 3 H), 2.10 (m, 1 H), 2.53 (m, 2H), 2.61 (m, 1H), 4.46 (dd, J=9.60, 4.40 Hz, 1 H), 4.97-5.07(m, 1H), 6.13 (s, 1H), 6.57(d, J=8.40 Hz, 1H), 7.40 (dd, J=8.40, 2.45 Hz, 1H), 7.72(s, 1H) and 8.36 (dd, J=5.20, 1.60 Hz, 1 H) ppm.
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Example 72. Preparation of *N*-(1-(6-aminopyridin-3-yl)-4-((1,1,1,3,3,3-

- 20 **hexafluoropropan-2-yl)oxy)-3-oxobutan-2-yl)-2-methoxy-2-methylpropanamide (72)**

- [0574] To a solution of compound **72.9** (10 g, 83.9 mmol, 1 *eq*) in THF (250 mL) was added LAH (6.37 g, 167.9 mmol, 2 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1.5 hour. The reaction mixture was quenched by addition saturated sodium sulfate at 0 °C and H₂O (200 mL) was added; then this was extracted with ethyl acetate (200 mL x 3). The combined
- 25 organic layers were washed with saturated brine (30mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the product compound **72.8** (6 g, crude) as a yellow solid. LCMS (ESI): *m/z*: [M + H]⁺ calcd for C₆H₇N₂O: 123; found 123; RT=0.276 min.

- [0575] To a solution of compound **72.8** (6 g, 49.14 mmol, 1 *eq*) in THF (100 mL) was
- 30 added TEA (19.89 g, 196.53 mmol, 4 *eq*), Boc₂O (32.16 g, 147.39 mmol, 3 *eq*) and DMAP



(1.2 g, 9.9 mmol, 0.2 *eq*). The mixture was stirred at 25°C for 12 hours. The reaction mixture was quenched by addition of H_2O (200 mL) at 25°C and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with saturated brines (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=3:1) to give compound **72.7** (5 g, 15.51 mmol, 32% yield) as a yellow solid. LCMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5$: 323; found 323; RT=1.532 min. ^1H NMR (400 MHz, chloroform-*d*) δ : 1.52 (br d, $J=3.97$ Hz, 28 H), 7.59 - 7.74 (m, 1 H), 8.10 - 8.28 (m, 1 H), 8.87 (br s, 1 H), 10.07 (br d, $J=3.97$ Hz, 1 H) ppm.

[0576] To a solution of compound **72.7** (5 g, 15.5 mmol, 1 *eq*) in DCM (60 mL) was added DBU (4.7 g, 30.4 mmol, 2 *eq*) and compound **72.6** (5.1 g, 15.5 mmol, 1 *eq*). The mixture was stirred at 25°C for 2 hours. The reaction mixture was quenched by addition of H_2O (100 mL) at 25°C and extracted with ethyl acetate (100 mL x 3). The combined organic layers

were washed with brine (5mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **72.5** (3 g, 5.7 mmol, 37 % yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₇H₃₄N₃O₈: 528; found 528; RT=1.604 min.

[0577] To a solution of compound **72.5** (3 g, 5.69 mmol, 1 *eq*) in MeOH (400 mL) was added 10% Pd on carbon catalyst (1 g) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was stirred under H₂ (50 psi) at 25 °C for 15 hours. The reaction mixture was filtered, and the filtrate was concentrated. compound **76.4** (1.5 g) was obtained as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₉H₃₀N₃O₆: 396; found 396; RT=1.084 min.

[0578] To a solution of 2-methoxy-2-methylpropanoic acid (448.09 mg, 3.79 mmol, 1 *eq*) in DMF (20 mL) was added HOBt (563.78 mg, 4.17 mmol, 1.1 *eq*) and EDCI (799.86 mg, 4.17 mmol, 1.1 *eq*). The mixture was stirred at 25 °C for 1 hr. To the mixture was added compound **72.4** (1.5 g, 3.79 mmol, 1 *eq*) and DIPEA (1.96 g, 15.17 mmol, 2.64 mL, 4 *eq*). The mixture was stirred at 25 °C for 14 hrs. The reaction mixture was quenched by addition of H₂O (30 mL) and was extracted with ethyl acetate (30mL x 3). The combined organic layers were washed with brine (5mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **72.3** (1.25 g, 2.52 mmol, 67% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₃₈N₃O₈: 496; found 496; RT=1.260 min.

[0579] To a solution of DIPA (1.40 g, 13.87 mmol, 1.96 mL, 5.5 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 5.55 mL, 5.5 *eq*). The mixture was stirred at 0 °C for 0.5 hr under N₂. The mixture was added to compound **72.3** (1.25 g, 2.52 mmol, 1 *eq*) and chloriodomethane (2.45 g, 13.87 mmol, 1.01 mL, 5.5 *eq*) in THF (10 mL) was stirred at -78 °C for 2.5 hrs. The reaction mixture was quenched by addition of saturated NH₄Cl (20 ml) at 25°C and extracted with ethyl acetate (15mL x 3). The combined organic layers were washed with saturated Na₂SO₃ (10 mL) and saturated NaHCO₃ (10 mL) and brine (10mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=0:1) to give compound **72.2**

(100 mg, 194.55 μ mol, 8% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₄H₃₇N₃O₇Cl: 514; found 514; RT=0.971 min.

[0580] To a solution of compound **72.2** (40 mg, 77.82 μ mol, 1 *eq*) in 1,1,1,3,3,3-hexafluoropropan-2-ol (800 mg, 4.76 mmol, 100 μ L, 61.18 *eq*) was added DIEA (60.35 mg, 466.92 μ mol, 81.33 μ L, 6 *eq*). The mixture was stirred at 25 °C for 12 hrs. The reaction mixture was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **72.1** (20 mg, 31 μ mol, 40% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₂H₃₀N₃O₆F₆: 646; found 546; RT=1.301 min.

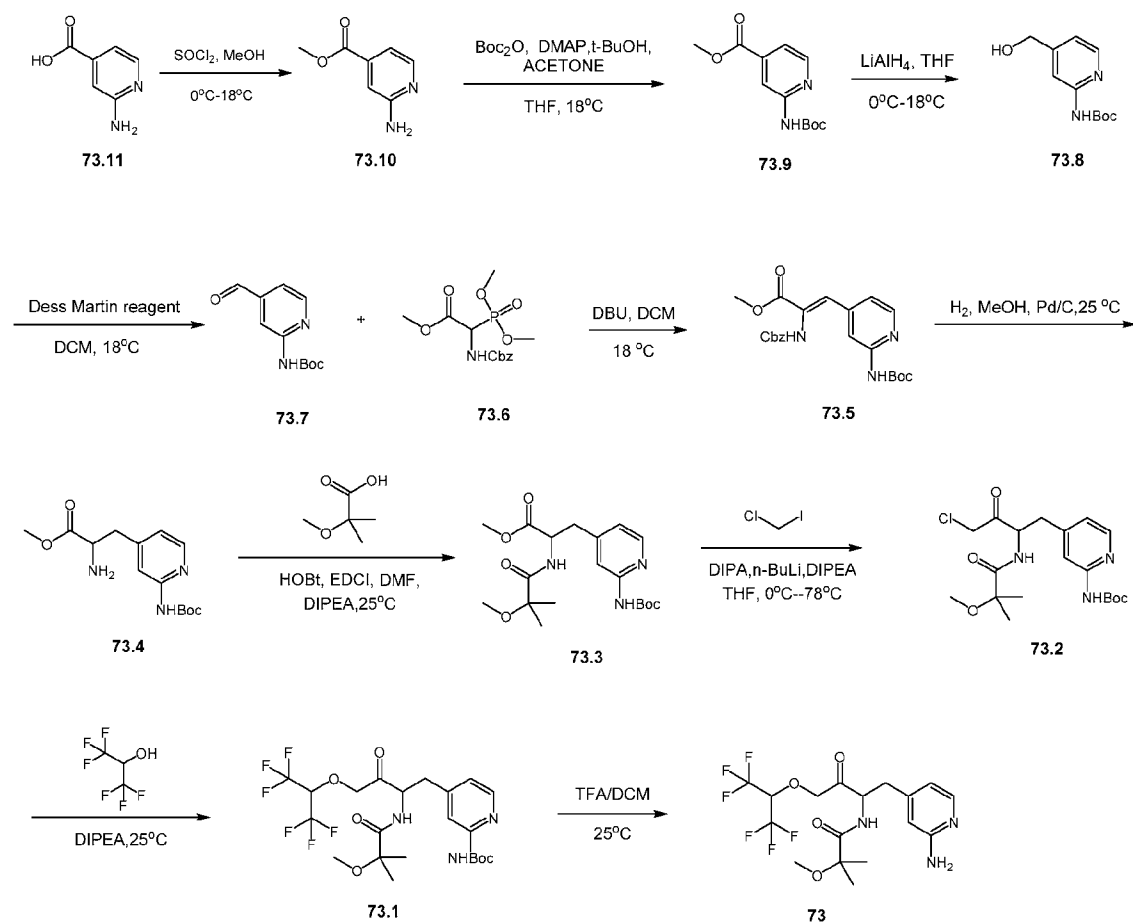
[0581] Compound **72.1** was added into DCM (5 mL) and TFA (1 mL), the mixture was stirred at 25 °C for 1 hour. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by semi-preparative scale HPLC (TFA condition) to give **72** (2 mg, 3.58 μ mol, 12% yield, TFA) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₇H₂₂N₃O₇F₆: 446; found 446; RT=0.925 min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 1.34 (d, *J*=9.54 Hz, 6 H), 2.23 (s, 3 H), 3.32 - 3.34 (m, 3 H), 4.91 - 4.95 (m, 3 H), 5.17 (dq, *J*=11.95, 6.04 Hz, 1 H), 6.92 (d, *J*=9.17 Hz, 1 H), 7.63 (s, 1 H) and 7.69 (dd, *J*=9.23, 2.02 Hz, 1 H) ppm.

Example 73. Preparation of *N*-(1-(2-aminopyridin-4-yl)-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-3-oxobutan-2-yl)-2-methoxy-2-methylpropanamide (73)

[0582] To a solution of compound **73.11** (50 g, 362 mmol, 1 *eq*) in MeOH (600 mL) was added SOCl₂ (172.27 g, 1.45 mol, 105.04 mL, 4 *eq*) drop wise at 0 °C under N₂, then stirred at 18 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to give compound **73.10** (60 g, crude) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₇H₉N₂O₂: 153; found 153; RT=0.214min.

[0583] To a mixture of compound **73.10** (60 g, 394.35 mmol, 1 *eq*) and DMAP (2.41 g, 19.72 mmol, 0.05 *eq*) in *t*-BuOH (600 mL) and ACETONE (200 mL) was added Boc₂O (344.26 g, 1.58 mol, 362.38 mL, 4 *eq*) dropwise. The mixture was stirred for 15 hours. The solution was diluted with pentane (200 ml), cooled in the refrigerator for 3 hours then filtered to give compound **73.9** (42 g, 166.49 mmol, 42% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₂H₁₇N₂O₄: 253; found 253; RT=1.562 min.

[0584] To a solution of compound **73.9** (42 g, 166.49 mmol, 1 *eq*) in THF (800 mL) was added LiAlH₄ (12.64 g, 332.98 mmol, 2 *eq*) portion wise at 0 °C under N₂. The mixture was



stirred at 0°C for 1 hours, then stirred for 14 hours. The reaction mixture was quenched by addition 8% NaOH (15ml), filtered and then diluted with H_2O (1000 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (1000 mL), 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/Ethyl acetate=2:1) to give compound **73.8** (15 g, 66.89 mmol, 40% yield) as a white solid. LCMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{11}\text{H}_{17}\text{N}_2\text{O}_3$: 225; found 225; RT =0.833min.

[0585] To a solution of compound **73.8** (15 g, 66.89 mmol, 1 *eq*) in DCM (150 mL) was added Dess-Martin periodinane (42.55 g, 100.33 mmol, 31.06 mL, 1.5 *eq*) portion-wise at 18°C under N_2 . The mixture was stirred for 2 hours. The reaction mixture was diluted with H_2O (60 mL) and extracted with DCM 150 mL (50 mL x 3). The combined organic layers were washed with brine (100 mL) (100 mL), 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/Ethyl acetate=5:1) to give compound **73.7** (9 g, 40.5 mmol, 61% yield) as a white solid.

[0586] To a mixture of compound **5** (2 g, 9 mmol, 1 *eq*) and compound **73.6** (2.98 g, 9 mmol, 1 *eq*) in DCM (20 mL) was added DBU (2.74 g, 18 mmol, 2.71 mL, 2 *eq*) in one portion. The mixture was stirred at 18 °C for 10 hours. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0:1) to give compound **73.5** (3 g, 7.02 mmol, 78% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ: 8.41 - 8.47 (m, 1 H), 8.39 - 8.49 (m, 1 H), 8.26 - 8.33 (m, 1 H), 8.25 - 8.33 (m, 1 H), 8.10 (br d, *J*=14.77 Hz, 1 H), 8.06 - 8.14 (m, 1 H), 7.32 - 7.50 (m, 5 H), 7.04 - 7.10 (m, 1 H), 7 (d, *J*=5.29 Hz, 1 H), 6.97 - 7.10 (m, 1 H), 6.85 (br d, *J*=4.41 Hz, 1 H), 6.76 - 6.91 (m, 1 H), 6.38 (s, 1 H), 5.17 (s, 1 H), 3.91 (s, 2 H), 3.95 (s, 1 H), 1.59 (s, 5 H) and 1.61 (s, 3 H) ppm.

[0587] To a solution of compound **73.5** (3 g, 7.02 mmol, 1 *eq*) in MeOH (300 mL) was added 10% palladium on carbon catalyst Pd/C (300 mg) under N₂. The suspension was degassed under vacuum and purged with H₂ several times. The mixture was shaken under H₂ (50 psi) at 25 °C for 20 hours. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by MPLC (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 1:1) to give compound **73.4** (1.4 g, 4.74 mmol, 68% yield) as a white solid. LCMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₄H₂₂N₃O₄: 296; found 296; RT=0.654 min.

[0588] To a mixture of 2-methoxy-2-methylpropanoic acid (560 mg, 4.74 mmol, 1 *eq*) and HOBt (704.6 mg, 5.21 mmol, 1.1 *eq*) in DMF (20 mL) was added EDCI (999.6 mg, 5.21 mmol, 1.1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 1 hour, then to the mixture was added compound **73.4** (1.4 g, 4.74 mmol, 1 *eq*) and DIPEA (1.84 g, 14.22 mmol, 2.48 mL, 3 *eq*) in one portion, and stirred at 25 °C for 9 hours. The reaction mixture was quenched by addition of H₂O (20 mL) and then extracted with EtOAc 60 mL (20 mL x 3). The combined organic layers were washed with H₂O (20 mL x 3) and brine (20 mL) then dried over Na₂SO₄, filtered and concentrated. The residue was purified by MPLC (SiO₂, Petroleum ether/Ethyl acetate=10/1 to 0:1) to give compound **73.3** (1.2 g, 3.03 mmol, 64% yield) as a white solid. ¹H NMR (400 MHz, chloroform-*d*) δ: 8.57 (s, 1 H), 8.18 (d, *J*=5.14 Hz, 1 H), 7.82 (s, 1 H), 7.09 (br d, *J*=8.19 Hz, 1 H), 6.74 (dd, *J*=5.26, 1.47 Hz, 1 H), 4.83 - 4.90 (m, 1 H), 3.77 (s, 3 H), 3.20 (s, 3 H), 3.17 (d, *J*=5.38 Hz, 1 H), 3.01 - 3.09 (m, 1 H), 1.52 (s, 9 H), 1.34 (s, 3 H) and 1.31 (s, 3 H) ppm.

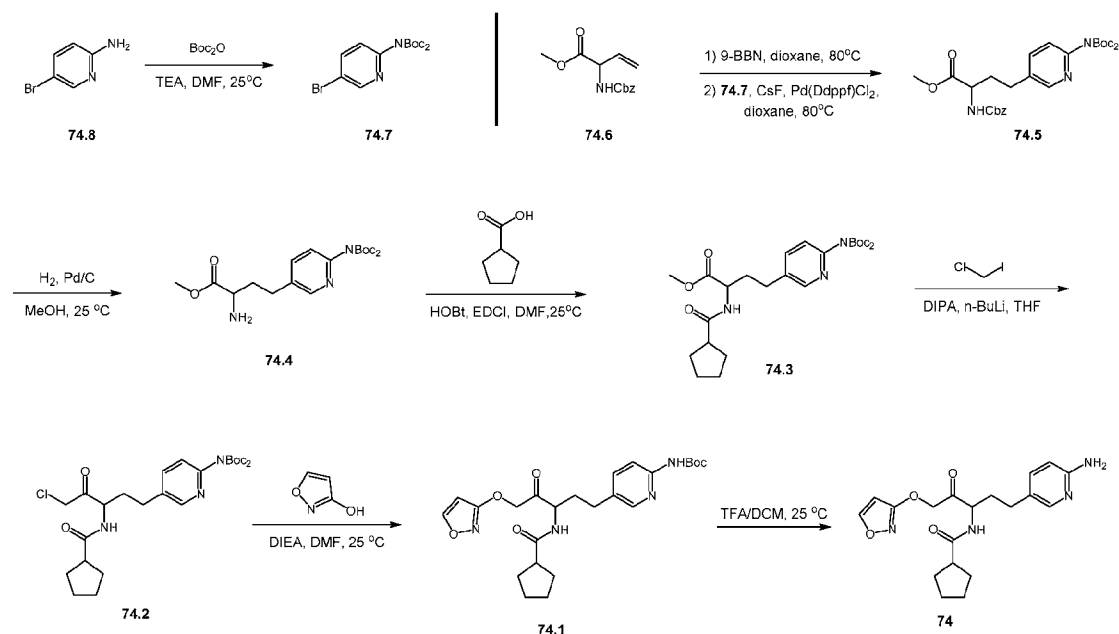
[0589] To a solution of DIPA (633.32 mg, 6.26 mmol, 884.52 μ L, 5.5 *eq*) in THF (20 mL) was added n-BuLi (2.5 M, 2.5 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins. To the mixture was added a solution of compound **73.3** (0.45 g, 1.14 mmol, 1 *eq*) and chloriodomethane (1.10 g, 6.26 mmol, 454.29 μ L, 5.5 *eq*) in THF (20 mL) at -78 °C. The mixture was stirred at -78 °C for 1.5h. The reaction mixture was quenched by addition of NH₄Cl (20 mL) and extracted with EtOAc (20 mL x 3), The combined organic layers were washed with saturated brines (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=1:1) to give compound **73.2** (100 mg, 241.61 μ mol, 21% yield) as a white solid.

[0590] To a solution of compound **73.2** (40 mg, 96.64 μ mol, 1 *eq*) in 1,1,1,3,3,3-hexafluoropropan-2-ol (64.96 mg, 386.57 μ mol, 100 μ L, 4 *eq*) was added DIPEA (0.5 M, 193.29 μ L, 1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 20 min. The residue was purified by semi-preparative scale HPLC (TFA condition) to give compound **73.1** (5 mg, 9.17 μ mol, 10% yield) as a white solid.

[0591] To a solution of compound **73.1** (5 mg, 9.17 μ mol, 1 *eq*) in DCM (2 mL) was added TFA (0.5 mL) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 1 min. Then the reaction mixture was concentrated under reduced pressure to give **73** (2 mg, 4.49 μ mol, 50% yield) as a white solid. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₇H₂₂F₆N₃O₄: 446; found 446; RT=2.635min. ¹H NMR (400 MHz, METHANOL-*d*₄) δ : 1.24 - 1.45 (m, 6 H), 2.29 (s, 2 H), 3.31 - 3.32 (m, 3 H), 3.39 - 3.53 (m, 2 H), 5.14 - 5.25 (m, 1 H), 6.71 (dd, *J*=6.72, 1.71 Hz, 1 H), 6.81 (s, 1 H) and 7.77 (d, *J*=6.72 Hz, 1 H) ppm.

Example 74. Preparation of N-(5-(6-aminopyridin-3-yl)-1-(isoxazol-3-yloxy)-2-oxopentan-3-yl)cyclopentanecarboxamide (74)

[0592] To a mixture of compound **74.8** (5 g, 28.9 mmol, 1 *eq*) and TEA (11.7 g, 115.6 mmol, 16.09 mL, 4 *eq*) in DMF (100 mL) was added Boc₂O (18.92 g, 86.7 mmol, 19.92 mL, 3 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction mixture was diluted with H₂O (100 mL) then was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue that remained was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5:1) to give compound **74.7**



(20 g, 53.58 mmol, 46% yield) as a white solid. ^1H NMR (400 MHz, chloroform- d) δ : 1.45 (s, 20 H), 7.18 (d, $J=8.44$ Hz, 1 H), 7.81 - 7.91 (m, 1 H), 7.81 - 7.91 (m, 1 H) and 8.54 (d, $J=2.20$ Hz, 1 H) ppm.

- 5 **[0593]** To a solution of compound **74.6** (3 g, 12.04 mmol, 1 *eq*) in dioxane (30 mL) was added 9-BBN (0.5 M, 53 mL, 2.2 *eq*) in one portion at 80°C under N_2 . The mixture was stirred at 80°C for 30 mins, then there was added CsF (5.48 g, 36.11 mmol, 1.33 mL, 3 *eq*), Pd(dppf) Cl_2 (880.65 mg, 1.2 mmol, 0.1 *eq*) and compound **74.7** (5.39 g, 14.44 mmol, 1.2 *eq*). This mixture was stirred at 80°C for 9.5 hours; then the reaction was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2 , Petroleum ether/Ethyl acetate=2:1) to give compound **74.5** (4 g, 7.36 mmol, 61% yield) as yellow oil. ^1H NMR (400 MHz, chloroform- d) δ : 1.44 (s, 18 H), 1.90 - 2.03 (m, 2 H), 2.11 - 2.26 (m, 1 H), 2.55 - 2.76 (m, 3 H), 3.66 - 3.80 (m, 4 H), 4.37 - 4.50 (m, 1 H), 5.08 - 5.18 (m, 2 H), 5.36 - 5.49 (m, 1 H), 7.14 (d, $J=7.89$ Hz, 1 H), 7.31 - 7.42 (m, 6 H), 7.55 (br d, $J=8.33$ Hz, 1 H) and 8.30 (s, 1 H) ppm.

- [0594]** To a solution of compound **74.5** (3.8 g, 6.99 mmol, 1 *eq*) in MeOH (100 mL) was added 10% Pd on carbon catalyst (400 mg) under N_2 . The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 atmosphere (50 psi) at 25°C for 0.5 hour. The reaction mixture was purged with N_2 gas, filtered through a Celite® pad and was concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=10:1 to 1:1) to give compound **74.4** (2 g, 4.88 mmol, 70% yield) as a yellow solid.

[0595] To a mixture of cyclopentanecarboxylic acid (111.5 mg, 976.86 μ mol, 106.19 μ L, 1 *eq*) and EDCI (206 mg, 1.07 mmol, 1.1 *eq*) in DMF (25 mL) was added HOBT (145.19 mg, 1.07 mmol, 1.1 *eq*) in one portion at 0 °C under N₂. The mixture was stirred at 0 °C for 1 hour. After this time, to the mixture was added dropwise a solution of compound **74.4** (400 mg, 976.86 μ mol, 1 *eq*) in DMF (5 mL), then there was added dropwise DIPEA (378.75 mg, 2.93 mmol, 510.44 μ L, 3 *eq*). This was stirred at 0 °C for 1 hour; then the reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3:1) to give compound **74.3** (2 g, 3.96 mmol, 81% yield) as a white solid. ¹H NMR (400 MHz, chloroform-d) δ : 1.44 (s, 15 H), 1.59 (br d, J=6.11 Hz, 2 H), 1.67 - 2 (m, 8 H), 2.12 - 2.28 (m, 1 H), 2.50 - 2.77 (m, 3 H), 3.66 - 3.82 (m, 3 H), 4.63 - 4.75 (m, 1 H), 6 - 6.12 (m, 1 H), 7.15 (d, J=8.07 Hz, 1 H), 7.51 - 7.61 (m, 1 H) and 8.29 (s, 1 H) ppm.

[0596] To a solution of DIPA (2.20 g, 21.76 mmol, 3.07 mL, 5.5 *eq*) in THF (10 mL) was added n-BuLi (2.5 M, 8.70 mL, 5.5 *eq*) at 0 °C, the mixture was stirred at 0 °C for 30 mins. To this mixture was added a solution of chloriodomethane (3.84 g, 21.76 mmol, 1.58 mL, 5.5 *eq*) and compound **74.3** (2 g, 3.96 mmol, 1 *eq*) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 30 mins. The reaction mixture was quenched by addition of NH₄Cl (20 mL) and then extracted with EtOAc 60 mL (20 mL x 3). The combined organic layers were washed with saturated aqueous Na₂SO₃ (30 mL), and brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=2:1) to give compound **74.2** (500 mg, 954.11 μ mol, 24% yield) as yellow oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₂₆H₃₉N₃O₆Cl: 525; found 525; RT=1.33 min.

[0597] To a mixture of compound **74.2** (500 mg, 954.11 μ mol, 1 *eq*) and isoxazol-3-ol (81.16 mg, 954.11 μ mol, 1 *eq*) in DMF (4 mL) was added DIEA (369.93 mg, 2.86 mmol, 498.56 μ L, 3 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 10 hours. The reaction was purified by prep-HPLC (TFA condition) to give compound **74.1** (100 mg, 211.63 μ mol, 22% yield) as yellow oil. ¹H NMR (400 MHz, chloroform-d) δ : 1.56 (s, 10

H), 1.62 (br s, 2 H), 1.70 - 1.83 (m, 4 H), 1.85 - 1.97 (m, 3 H), 2.24 - 2.36 (m, 1 H), 2.56 - 2.66 (m, 1 H), 2.70 (br t, J=7.95 Hz, 2 H), 4.82 - 4.89 (m, 1 H), 4.92 - 5.07 (m, 2 H), 6.08 (s, 1 H), 6.22 (br d, J=7.70 Hz, 1 H), 7.92 (br d, J=9.29 Hz, 1 H), 7.99 (s, 1 H), 8.17 (s, 1 H) and 8.35 (d, J=8.68 Hz, 1 H) ppm.

- 5 [0598] To a solution of compound **74.1** (100 mg, 211.63 μ mol, 1 *eq*) in DCM (5 mL) was added TFA (211.63 μ mol, 15.67 μ L, 1 *eq*) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 1 hour. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by semi-preparative scale HPLC (TFA condition) to give **74** (40 mg, 107.41 μ mol, 51% yield) as colorless oil. LCMS (ESI) m/z: [M + H]⁺ calcd for C₁₉H₂₅N₄O₄: 373; found 373; RT=2.046 min. ¹H NMR (400 MHz, METHANOL-d₄) δ : 1.56 - 1.67 (m, 2 H), 1.69 - 1.81 (m, 4 H), 1.84 - 1.97 (m, 3 H), 2.14 - 2.25 (m, 1 H), 2.53 - 2.81 (m, 3 H), 4.49 (dd, J=9.17, 4.77 Hz, 1 H), 4.95 - 5.11 (m, 2 H), 6.15 (d, J=1.83 Hz, 1 H), 6.99 (d, J=9.17 Hz, 1 H), 7.65 (d, J=1.34 Hz, 1 H), 7.88 (dd, J=9.17, 2.20 Hz, 1 H) and 8.37 (d, J=1.83 Hz, 1 H) ppm.
- 10

15 **Example 75. Inhibition of arginine gingipain by the aminopyridinecyanamide compounds of the invention.**

- [0599] The capacities of compounds of the present invention to inhibit the activity of RgpB were measured in a fluorogenic assay similar to those described in Barret *Biochemical Journal*. **1980**, 187(3), 909. The specific assay conditions were as follows. Buffer: pH = 7.5, 20 100 mM Tris-HCl, 75 mM NaCl, 2.5 mM CaCl₂, 10 mM cysteine, 1% DMSO after all additions. Protein: 0.02 nM RgpB, isolated from culture of *Porphyromonas gingivalis*, as described in Pike *et al. J. Biol. Chem.* **1994**, 269(1), 406, and Potempa and Nguyen. *Current Protocols in Protein Scienc.* **2007**, 21.20.1-21.20.27. Fluorogenic substrate: 10 μ M Boc-Phe-Ser-Arg-MCA. Time = 90 minutes. Temperature = 37 °C. Each compound: 10 25 concentrations, starting at either 100 μ M or 100 nM, with lower concentrations generated by serial 3-fold dilutions. By testing a range of concentrations for each compound, the concentration required to inhibit the activity of RgpB by 50% (the "IC₅₀") was determined. RgpB inhibitory activity is summarized in the following table.

No.	Activity	No.	Activity	No.	Activity
1	+	27	+	51b	++
2	++++	28	+++	52a	>1 μM^a
3	++++	29	++	52b	>1 μM^a
4	++	30	++	53	+++++
5	++	31	+	54	+++++
6	++	32	++++	55	+++++
7	+	33	+++	56	+++++
8	+	34	+++	57	+++++
9	++++	35	+++	58	++++
10	+	36	+++	59	++++
11	+	37	++++	60	+++++
12	++++	38	++	61	+++++
13	++++	39	++	62	++++
14	++++	40	++	63	+++
15	++++	41	++	64	++++
16	++	42	++	65	+++++
17	+++	43	+++++	66	+++++
18	++	44	++++	67	+++++
19	+++++	45	+++++	68	+++++
20	+++	46	+++	69	+++++
21	++++	47	+++	70	++++
22	++++	48	++++	71	++++
23	++	49	+++++	72	>1 μM^a
24	++	50a	+++++	73	>1 μM^a
25	++++	50b	+++++	74	+++++
26	++++	51a	++		

+++++ : RgpB $\text{IC}_{50} < 100 \text{ nm}$

++++ : $100 \text{ nM} \leq \text{RgpB } \text{IC}_{50} < 1 \mu\text{M}$

+++ : $1 \mu\text{M} \leq \text{RgpB } \text{IC}_{50} < 10 \mu\text{M}$

++ : $10 \mu\text{M} \leq \text{RgpB } \text{IC}_{50} < 100 \mu\text{M}$

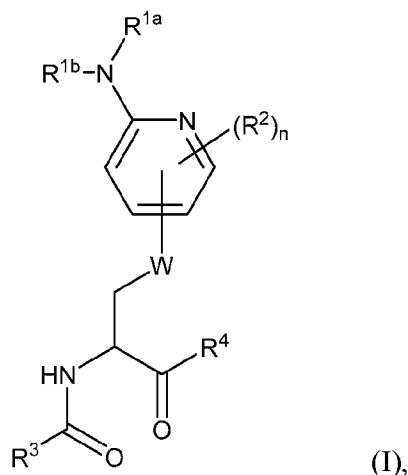
+: $100 \mu\text{M} \leq \text{RgpB } \text{IC}_{50}$

^a compound not tested above $1 \mu\text{M}$

[0600] Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity and understanding, one of skill in the art will appreciate that certain changes and modifications can be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



or a pharmaceutically acceptable salt thereof, wherein

W is selected from the group consisting of a bond, CH₂, and O;

R^{1a} and R^{1b} are independently selected from the group consisting of H and C₁₋₆ alkyl;

R² is selected from the group consisting of C₁₋₆ alkyl and halogen;

subscript n is 0 or 1;

R³ is selected from the group consisting of C₃₋₈ cycloalkyl, C₃₋₈ alkyl,

C₃₋₁₂ heterocyclyl, C₆₋₁₀ aryl, and C₅₋₁₂ heteroaryl wherein R³ is optionally

substituted with one or more R^{3a} substituents;

each R^{3a} is independently selected from the group consisting of

halogen, -CN, -NO₂, -N₃, -OH, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₁₋₄ alkoxy,

C₁₋₄ haloalkoxy, -N(R^c)₂, -(CH₂)_kC(O)R^b, -NR^c(CH₂)_uC(O)R^b, -O(CH₂)_uC(O)R^b

, -(CH₂)_kCONR^cR^c, -(CH₂)_kNR^cC(O)R^b, -NR^c(CH₂)_uCONR^cR^c, -NR^c(CH₂)_uN

R^cC-(O)R^b, -O(CH₂)_uCONR^cR^c, and -O(CH₂)_uNR^cC(O)R^b, and optionally

substituted triazolyl;

each R^b is independently selected from the group consisting of C₁₋₄ alkyl,

C₁₋₄ haloalkyl, and C₁₋₄ deuterioalkyl;

each R^c is independently selected from the group consisting of hydrogen and

C₁₋₈ alkyl;

each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6;

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6;

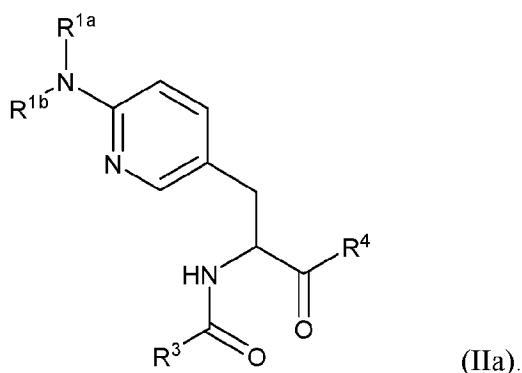
R⁴ is selected from the group consisting of -CH₂R^{4a} and C₁₋₆ haloalkyl;

R^{4a} is selected from the group consisting of $-O-R^5$, $-S-R^6$, $-SO-R^6$, $-SO_2-R^6$, $-N(R^7)_2$,
 and C_{5-12} heteroaryl;
 R^5 is selected from the group consisting of phenyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and
 C_{5-12} heteroaryl, wherein phenyl is substituted with 1-5 halogens, and wherein
 C_{5-12} heteroaryl is optionally substituted with halogen or C_{1-3} haloalkyl;
 R^6 is selected from the group consisting of phenyl, C_{1-6} alkyl, C_{1-6} haloalkyl, and
 C_{5-12} heteroaryl, wherein phenyl is optionally substituted with 1-5 halogens,
 and wherein C_{5-12} heteroaryl is optionally substituted with halogen or
 C_{1-3} haloalkyl; and
 each R^7 is independently selected C_{1-6} alkyl.

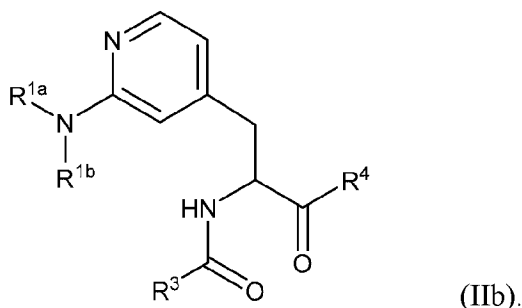
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is a bond.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein W is selected from the group consisting of CH_2 and O.

4. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, having a structure according to Formula IIa:



5. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, having a structure according to Formula IIb:



1 6. The compound of any one of claims 1-5, or a pharmaceutically
2 acceptable salt thereof, wherein R^3 is selected from the group consisting of C_{3-8} cycloalkyl
3 and C_{3-8} alkyl, each of which is optionally substituted with one or more R^{3a} substituents.

1 7. The compound of any one of claims 1-7, or a pharmaceutically
2 acceptable salt thereof, wherein R^3 is selected from the group consisting of cyclopentyl and
3 isopropyl.

1 8. The compound of claim 1, or a pharmaceutically acceptable salt
2 thereof, wherein R^3 is unsubstituted cyclopentyl.

1 9. The compound of claim 7, or a pharmaceutically acceptable salt
2 thereof, wherein R^3 is unsubstituted cyclopentyl.

1 10. The compound of claim 1, or a pharmaceutically acceptable salt
2 thereof, wherein R^3 is isopropyl and R^{3a} is methoxy.

1 11. The compound of claim 7, or a pharmaceutically acceptable salt
2 thereof, wherein R^3 is isopropyl and R^{3a} is methoxy.

1 12. The compound of claim 1, or a pharmaceutically acceptable salt
2 thereof, wherein R^4 is $-CH_2-O-R^5$ and wherein R^5 is phenyl substituted with 1-5 halogens.

1 13. The compound of claim 12, or a pharmaceutically acceptable salt
2 thereof, wherein each halogen in R^5 is F.

1 14. The compound of any one of claims 1-11, or a pharmaceutically
2 acceptable salt thereof, wherein R^4 is $-CH_2-O-R^5$ and R^5 is selected from the group consisting
3 of 1,1,1,3,3,3-hexafluoroprop-2-yl, isoxazolyl, and phenyl, wherein phenyl is substituted with
4 1-5 halogens.

1 15. The compound of claim 14, or a pharmaceutically acceptable salt
2 thereof, wherein R^5 is phenyl substituted with 1-5 halogens.

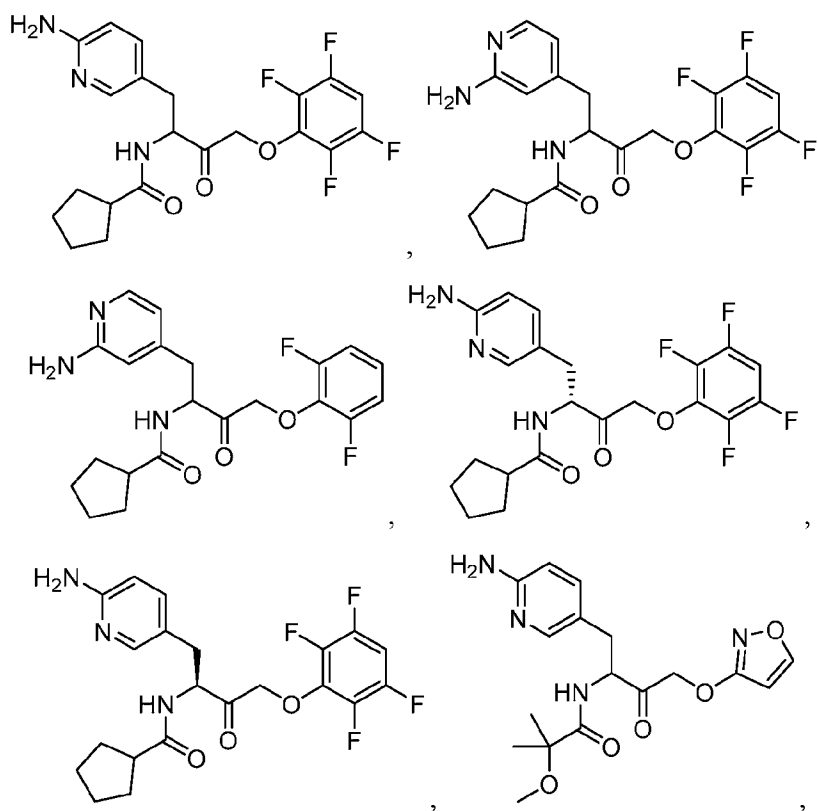
1 16. The compound of claim 15, or a pharmaceutically acceptable salt
2 thereof, wherein each halogen in R^5 is selected from the group consisting of F and Cl.

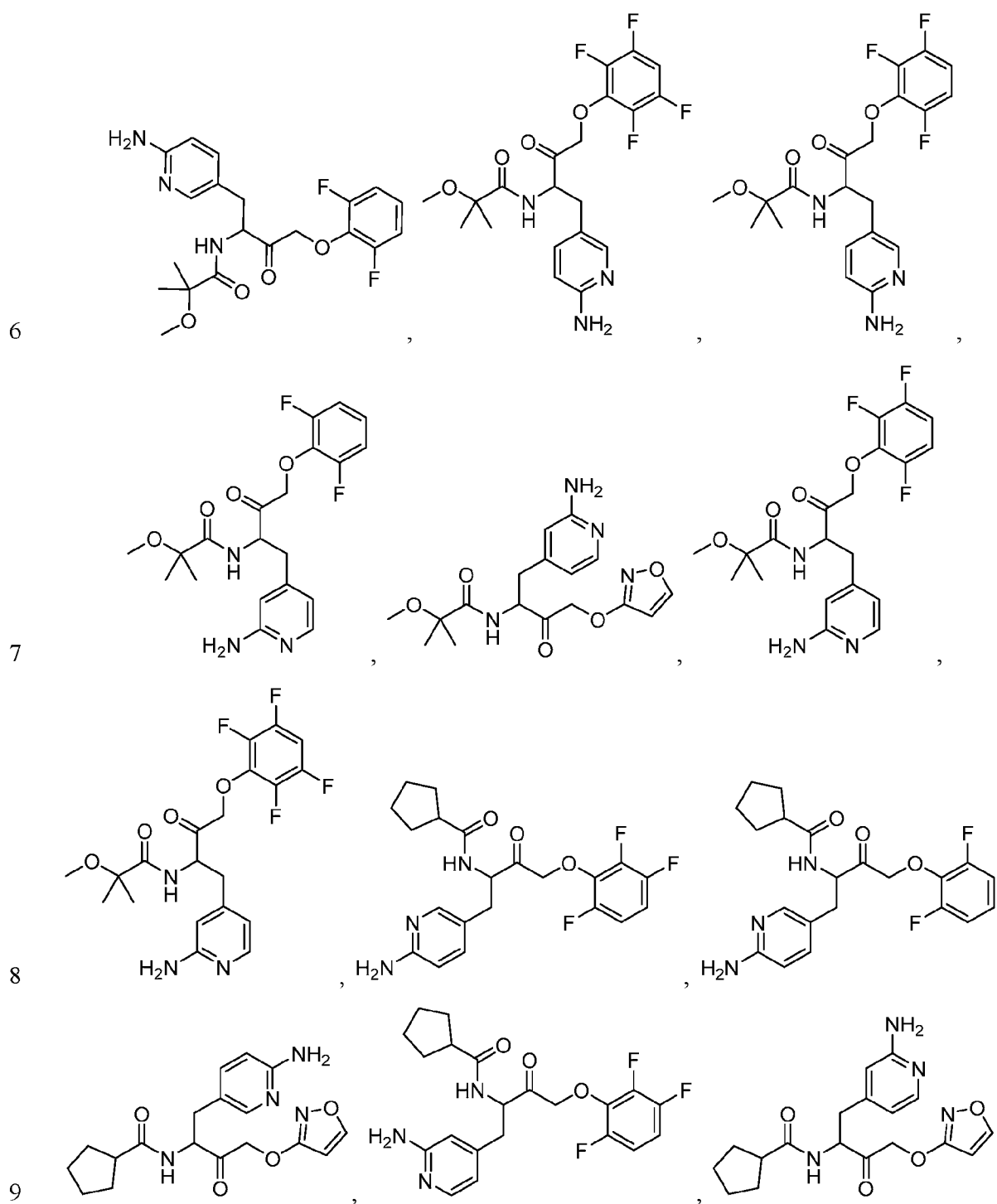
1 17. The compound of claim 16, or a pharmaceutically acceptable salt
2 thereof, wherein each halogen in R⁵ is F.

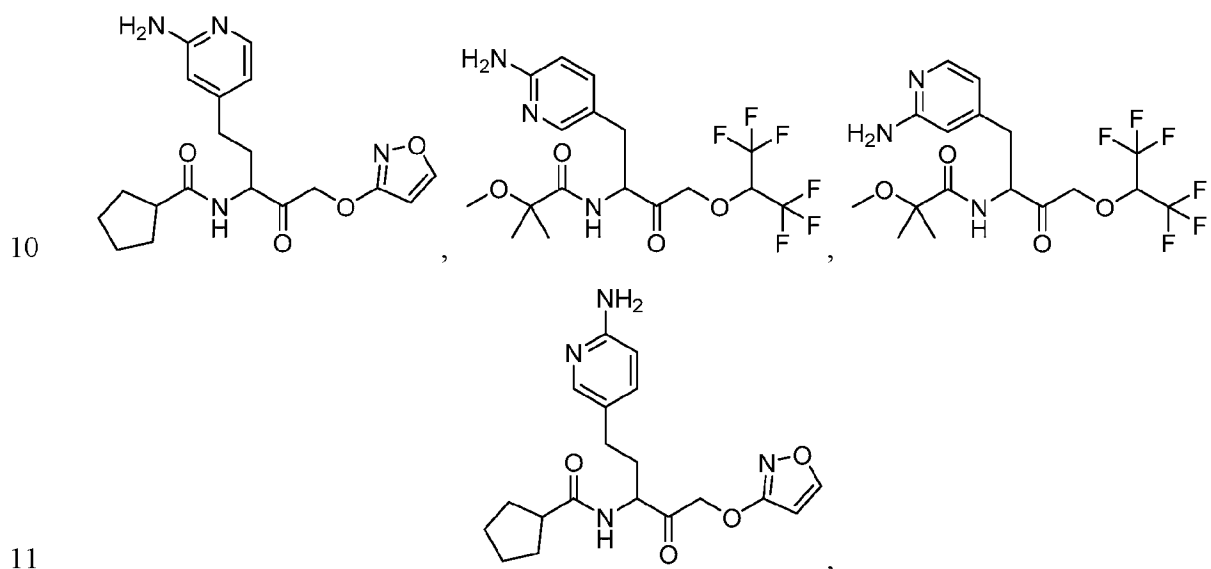
1 18. The compound of any one of claims 14-17, or a pharmaceutically
2 acceptable salt thereof, wherein R⁵ is selected from the group consisting of 2-fluorophenyl; 3-
3 fluorophenyl; 4-fluorophenyl; 2,3-difluorophenyl; 2,4-difluorophenyl; 2,5-difluorophenyl;
4 2,6-difluorophenyl; 3,4-difluorophenyl; 3,5-difluorophenyl; 2,3,4-trifluorophenyl; 3,4,5-
5 trifluorophenyl; 2,3,6-trifluorophenyl; 2,3,5-trifluorophenyl; and 2,3,5,6-tetrafluorophenyl.

1 19. The compound of claim 18, or a pharmaceutically acceptable salt
2 thereof, wherein R⁵ is selected from the group consisting of 2,6-difluorophenyl; 2,3,6-
3 trifluorophenyl; and 2,3,5,6-tetrafluorophenyl.

1 20. The compound of claim 1, which is selected from the group consisting
2 of

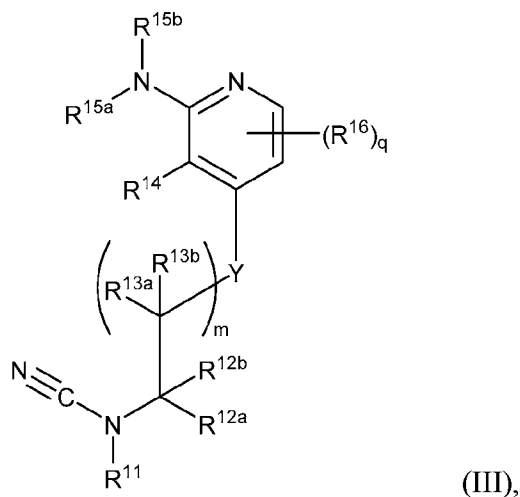






and pharmaceutically acceptable salts thereof.

21. A compound according to Formula III:



or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is selected from the group consisting of C_{1-6} alkyl and C_{3-8} cycloalkyl;

R^{12a} and R^{12b} are independently selected from the group consisting of H, C_{1-6} alkyl, and C_{6-10} aryl, or

R^{12a} and R^{12b} are taken together to form C_{3-6} cycloalkyl, or

R^{12a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl which is optionally substituted with one or more R^{17} ;

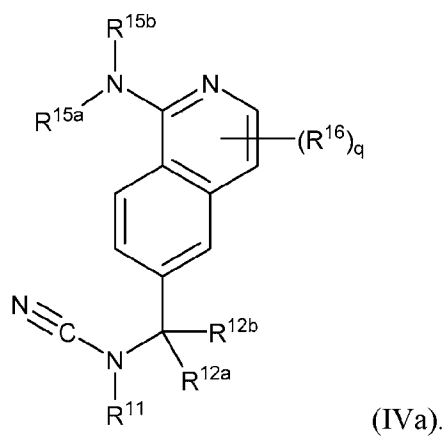
each R^{13a} and each R^{13b} is independently selected from the group consisting of

H, -OH, and C_{1-6} alkyl, or

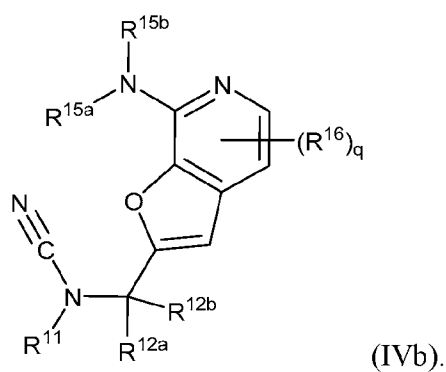
one R^{13a} and R^{11} are taken together to form 4- to 10-membered heterocyclyl,

13 or
14 one R^{13b} and R^{12b} are taken together to form a 5- or 6-membered ring;
15 R¹⁴ is selected from the group consisting of H and halogen, or
16 R¹⁴, R^{12a}, and R^{12b} are taken together to form a 6- to 8-membered ring, which
17 is optionally substituted with one or more R¹⁸, or
18 R¹⁴ and one R^{13a} are taken together to form a 5- to 8-membered ring, which is
19 optionally substituted with one or more R¹⁸, or
20 R¹⁴ is taken together with one R^{13a} and one R^{13b} on the same carbon atom to
21 form a 5- to 8-membered ring, which is optionally substituted with one or
22 more R¹⁸, or
23 R¹⁴, R¹¹, and R^{12a} are taken together to form a 6- to 10-membered bicyclic
24 ring, which is optionally substituted with one or more R¹⁸;
25 R^{15a} and R^{15b} are independently selected from the group consisting of H and
26 C₁₋₆ alkyl;
27 R¹⁶ is independently selected from the group consisting of C₁₋₆ alkyl and halogen;
28 each R¹⁷ is independently selected from the group consisting of C₁₋₆ alkyl,
29 C₁₋₆ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, -OH, and -N(R^{17a})₂, wherein each
30 R^{17a} is independently selected from the group consisting of H and C₁₋₆ alkyl;
31 each R¹⁸ is independently selected from the group consisting of C₁₋₆ alkyl and
32 halogen;
33 Y is selected from the group consisting of O, S, C(R^{19a})₂, and NR^{19b};
34 each R^{19a} is selected from the group consisting of H and C₁₋₆ alkyl, or
35 one R^{19a} and one R^{13b} on adjacent atoms are taken together to form a double
36 bond;
37 R^{19b} is selected from the group consisting of H and C₁₋₆ alkyl, or
38 R^{19b} and R¹¹ are taken together to form a 4- to 6-membered ring;
39 subscript m is 0, 1, 2, or 3; and
40 subscript q is 0 or 1.

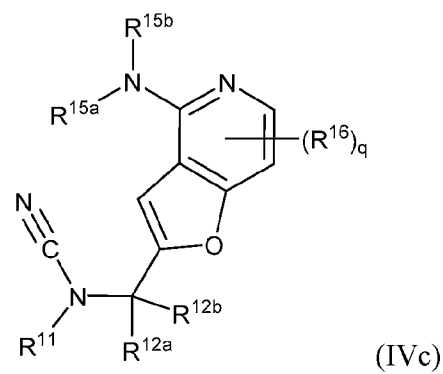
1 22. The compound of claim 21, or a pharmaceutically acceptable salt
2 thereof, having a structure according to Formula IVa:



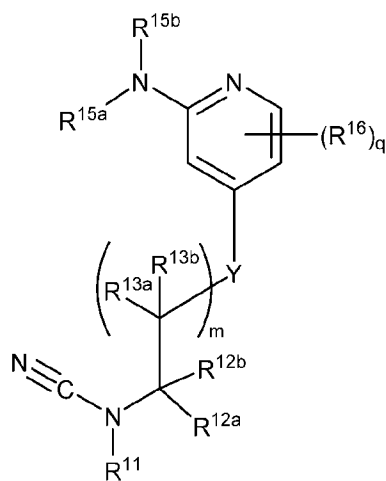
23. The compound of claim 21, or a pharmaceutically acceptable salt thereof, having a structure according to Formula IVb:



24. The compound of claim 21, or a pharmaceutically acceptable salt thereof, having a structure according to Formula IVc:



25. The compound of claim 21, or a pharmaceutically acceptable salt thereof, having a structure according to Formula V:



(V).

26. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein Y is O or S.

27. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein Y is CH₂.

28. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein Y is CH(R^{19a}), R^{19a} and R^{13b} are taken together to form a double bond, and subscript m is 1.

29. The compound of claim 25, or a pharmaceutically acceptable salt thereof, wherein Y is NR^{19b}, and wherein R^{19b} and R¹¹ are taken together to form a 5- or 6-membered ring.

30. The compound of any one of claims 21-28, or a pharmaceutically acceptable salt thereof, wherein R^{12a} and R¹¹ are taken together to form 4- to 10-membered heterocyclyl.

31. The compound of claim 30, or a pharmaceutically acceptable salt thereof, wherein R^{12a} and R¹¹ are taken together to form azetidin-1,2-diyl, pyrrolidin-1,2-diyl, piperidin-1,2-diyl, indolin-1,2-diyl, or isoindolin-1,2-diyl.

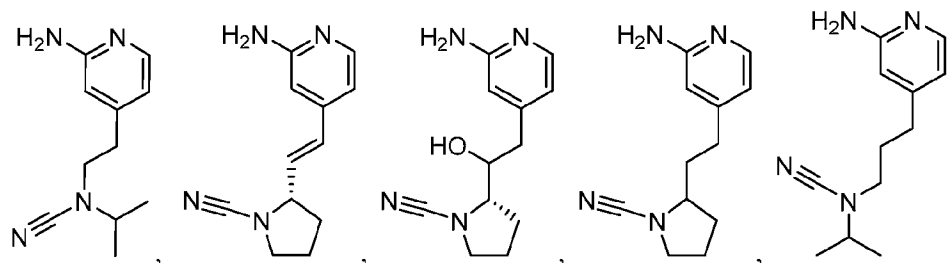
32. The compound of any one of claims 21-29, or a pharmaceutically acceptable salt thereof, wherein R^{12a} is H and R^{12b} is selected from the group consisting of H, C₁₋₆ alkyl, and C₆₋₁₀ aryl.

33. The compound of claim 32, or a pharmaceutically acceptable salt thereof, wherein R^{11} is C_{1-6} alkyl.

34. The compound of any one of claims 21-33, or a pharmaceutically acceptable salt thereof, wherein R^{15a} and R^{15b} are H.

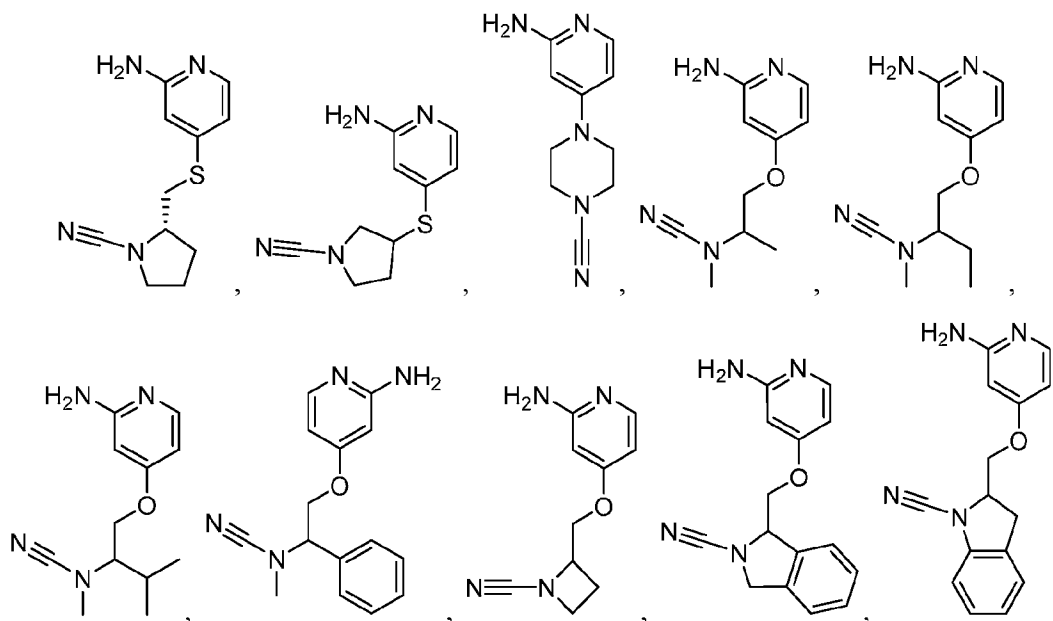
35. The compound of any one of claims 21-33, or a pharmaceutically acceptable salt thereof, wherein subscript q is 0.

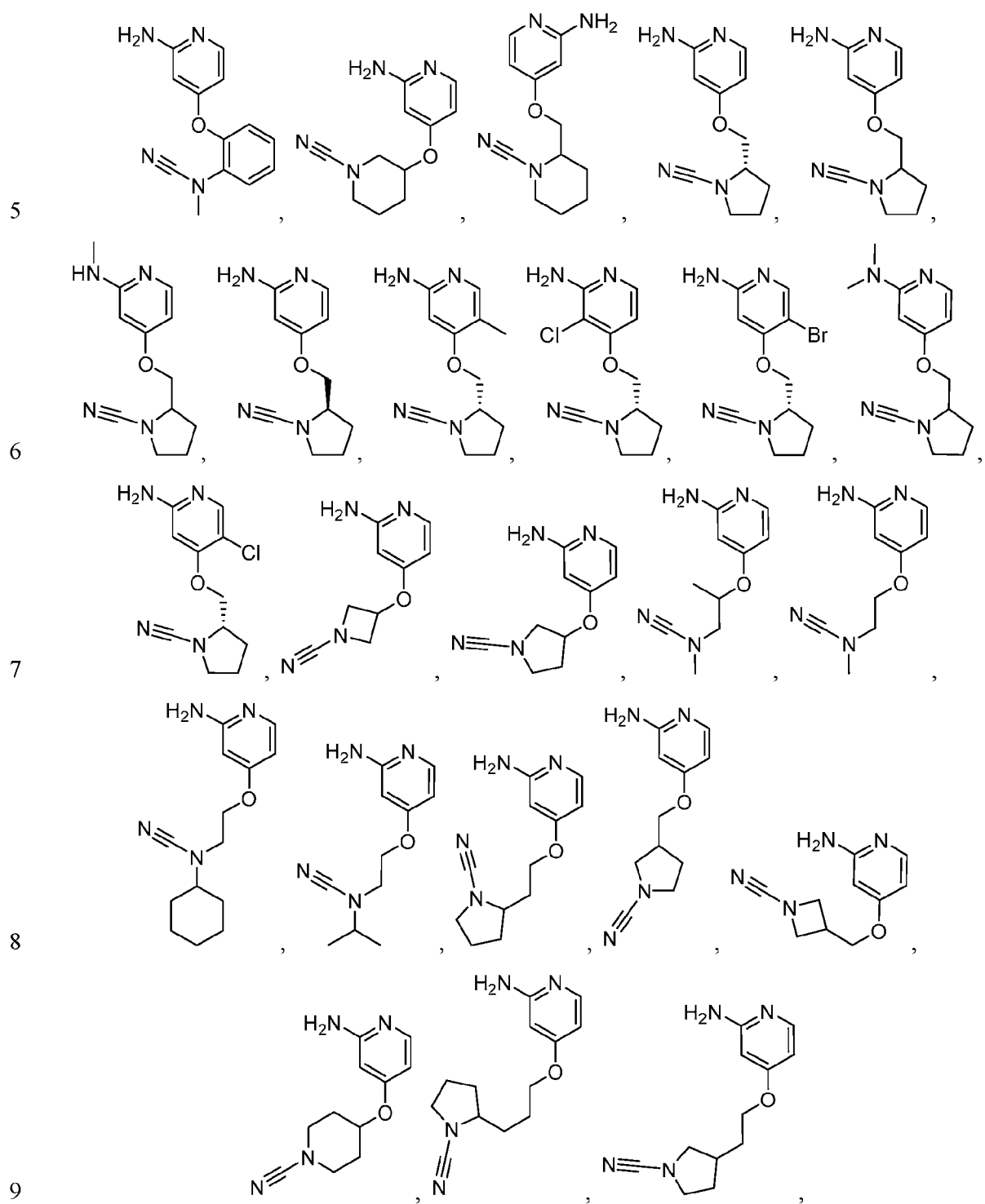
36. The compound of claim 21, which is selected from the group consisting of:



and pharmaceutically acceptable salts thereof.

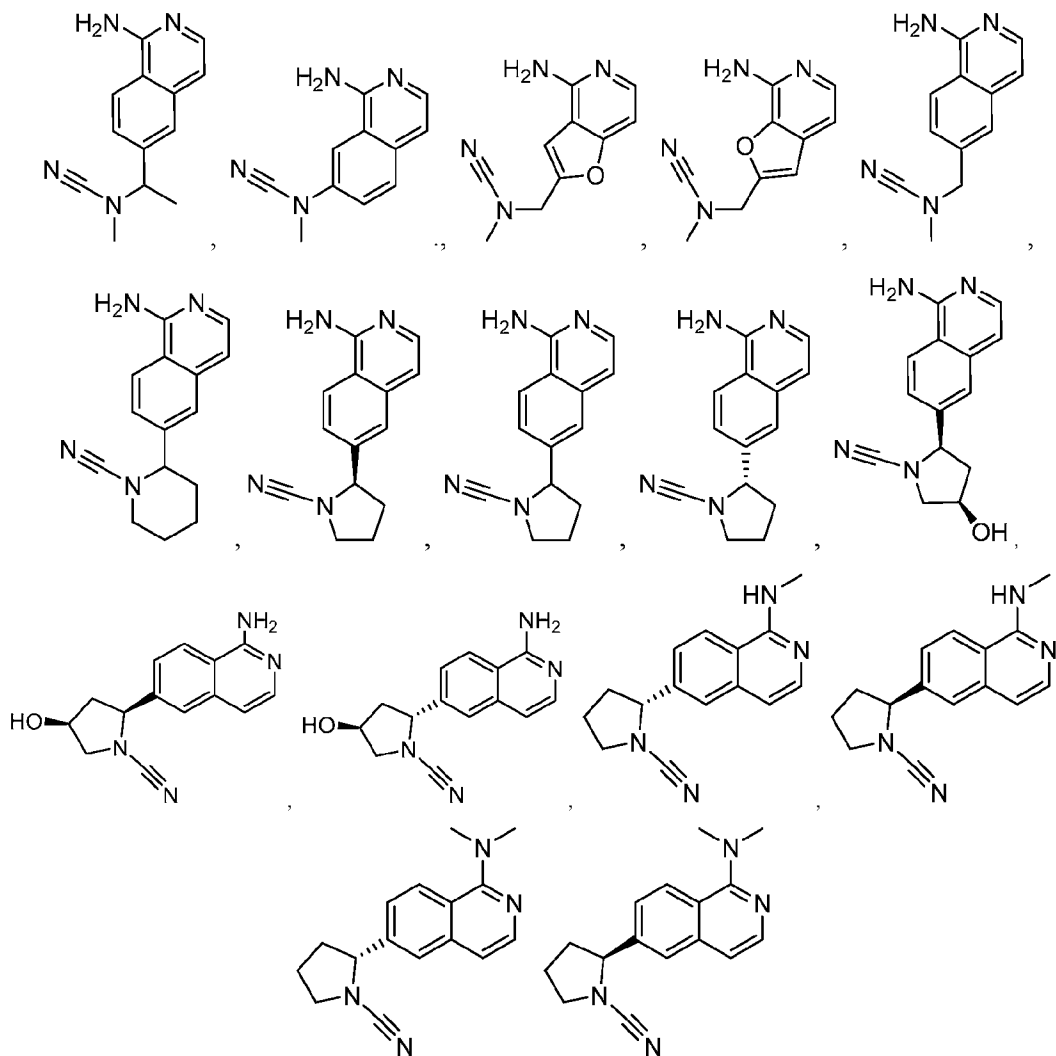
37. The compound of claim 21, which is selected from the group consisting of:





and pharmaceutically acceptable salts thereof.

38. The compound of claim 21, which is selected from the group consisting of:



and pharmaceutically acceptable salts thereof.

39. A pharmaceutical composition comprising a compound of any one of claims 1-38, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

40. A method of inhibiting a gingipain, the method comprising contacting the gingipain with an effective amount of a compound according to any one of claims 1-38.

41. The method of claim 40, wherein the gingipain is an arginine gingipain.

1 42. A method of treating a disease or condition associated with *P.*
2 *gingivalis* infection, the method comprising administering to a subject in need thereof an
3 effective amount of a compound according to any one of claims 1-38, or a pharmaceutically
4 acceptable salt thereof, or an effective amount of a composition according to claim 39.

1 43. The method of claim 42, wherein the disease or condition is selected
2 from the group consisting of a brain disorder, periodontal disease, diabetes, a cardiovascular
3 disease, arthritis, rheumatoid arthritis, osteoarthritis, infectious arthritis, psoriatic arthritis,
4 elevated risk of preterm birth, pneumonia, cancer, a kidney disease, a liver disease, a retinal
5 disorder, and glaucoma.

1 44. The method of claim 43, wherein the disease or condition is a brain
2 disorder.

1 45. The method of claim 44, wherein the brain disorder is selected from
2 the group consisting of Alzheimer's disease, Down's syndrome, epilepsy, autism, Parkinson's
3 disease, essential tremor, fronto-temporal dementia, progressive supranuclear palsy,
4 amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, mild cognitive
5 impairment, age associated memory impairment, chronic traumatic encephalopathy, stroke,
6 cerebrovascular disease, Lewy Body disease, multiple system atrophy, schizophrenia, and
7 depression.

1 46. The method of claim 45, wherein the brain disorder is Alzheimer's
2 disease.

1 47. The method of claim 46, further comprising administering to the
2 subject one or more active agents selected from the group consisting of a cholinesterase
3 inhibitor, a serotonin modulator, an NMDA modulator, an A β targeted therapy, an ApoE
4 targeted therapy, a microglia targeted therapy, a blood brain barrier targeted therapy, a tau
5 targeted therapy, a complement targeted therapy, and an anti-inflammatory.

1 48. The method of claim 43, wherein the disease or condition is
2 periodontal disease.

1 49. The method of claim 43, wherein the disease or condition is a liver
2 disease.

- 1 50. The method of claim 49, wherein the liver disease is non-alcoholic
2 steatohepatitis.
- 1 51. The method of claim 43, wherein the disease or condition is a retinal
2 disorder.
- 1 52. The method of claim 51, wherein the retinal disorder is age-related
2 macular degeneration.
- 1 53. The method of claim 43, wherein the disease or condition is cancer.
- 1 54. The method of claim 53, wherein the cancer is selected from the group
2 consisting of oral cancer, breast cancer, pancreatic cancer, and glioblastoma multiforme.
- 1 55. The method of claim 43, wherein the disease or condition is elevated
2 risk of preterm birth.
- 1 56. The method of claim 43, wherein the disease or condition is arthritis.
- 1 57. The method of claim 56, wherein the arthritis is rheumatoid arthritis or
2 osteoarthritis.
- 1 58. The method of claim 43, wherein the disease or condition is a
2 cardiovascular disease.
- 1 59. The method of claim 43, wherein the disease or condition is diabetes.
- 1 60. The method of any one of claims 42-59, wherein the compound is
2 administered to the subject for at least one month.
- 1 61. The method of claim 60, wherein the compound is administered to the
2 subject for at least one year.
- 1 62. The method of claim 60, wherein the compound is administered to the
2 subject for at least 10 years.
- 1 63. The method of claim 60, wherein the compound is administered to the
2 subject for at least 60 years.

- 1 64. The method of any one of claims 42-63, wherein the subject is a
2 human, a canine, or a feline.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/32139

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A61K 31/44; C07D 213/72; 401/12 (2018.01)
 CPC - A61K 31/44; C07D 213/75; C07D 401/12

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 2016/0096830 A1 (CORTEXIME, INC.) 07 April 2016 (07.04.2016) pg. 34, Table 1, Compound 43	1-5; 8-13; 20
A	Bialas et al. Exploring the Sn Binding Pockets in Gingipains by Newly Developed Inhibitors: Structure-Based Design, Chemistry, and Activity in J. Med. Chem. 2006, Vol. 49, pp. 1744-1753. pg. 1747, Figure 3, Compound 2F	1-5; 8-13; 20
A	US 2003/0008829 A1 (COSTANZO et al.) 09 January 2003 (09.01.2003) pg.10, Compound 35	1-5; 8-13; 20
A	WO 00/53172 A1 (SMITHKLINE BEECHAM CORPORATION) 14 September 2000 (14.09.2000) pg. 6, Scheme 1, product; pg. 10, Example 1	1-5; 8-13; 20
A	WO 2016/046530 A1 (MISSION THERAPEUTICS LTD) 31 March 2016 (31.03.2016) pg. 102, line 27, example 71	21-33; 36-38
A	PUBCHEM 104185245 deposited on 13 January 2016 (13.01.2016) pp. 1-9. pg. 3	21-33; 36-38
A	PUBCHEM 106640197 deposited 15 January 2016 (15.01.2016) pp. 1-9. pg 3	21-33; 36-38
A	US 2016/0347715 A1 (SUNIL ABRAHAM DAVID et al.) 01 December 2016 (01.12.2016) para [0102];[0103]	21-33; 36-38

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

☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

07 JULY 2018

Date of mailing of the international search report

01 AUG 2018

Name and mailing address of the ISA/US

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 18/32139

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.: 6-7, 14-19, 34-35 and 39-64
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:

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.:

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.