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(54) Title: SMALL MOLECULES THAT TARGET THE RNA THAT CAUSES ALS

(57) Abstract: Disclosed herein are compounds that selectively bind an expanded transcribed repeat $r(G_4C_2)^{exp}$, prevent sequestration of RNA-binding proteins, and inhibit translation of repeat associated non-ATG (RAN) translation responsible for generation of toxic dipeptide repeats underlying diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The compounds and their pharmaceutical compositions are useful in treating a disease or condition characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$), such as ALS and FTD.

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SMALL MOLECULES THAT TARGET THE RNA THAT CAUSES ALS

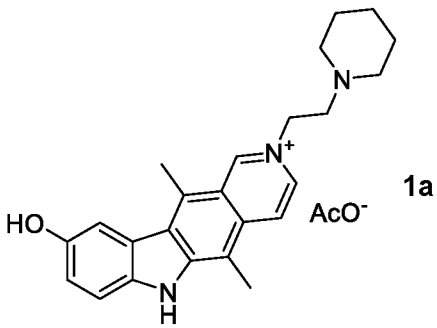
STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under grants Nos. DP1 NS096898-02, P01 NS099114-01, and R35NS097273, awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

BACKGROUND

[0002] Amyotrophic lateral sclerosis (ALS), a devastating neurodegenerative disorder caused by progressive loss of motor neurons, often results in paralysis and death within three to five years of onset (Taylor et al., 2016). Current treatment options for ALS remain scarce and are only palliative (Taylor et al., 2016). With the discovery that an expanded, transcribed G_4C_2 repeat in *C9ORF72* is the most common genetic cause of ALS and frontotemporal dementia (FTD) ("c9ALS/FTD"), a new therapeutic target has emerged (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The transcribed repeat RNA ("$r(G_4C_2)^{exp}$") plays an essential role in two putative pathological mechanisms: (i) sequestering proteins involved in RNA biogenesis to form toxic $r(G_4C_2)^{exp}$–protein foci (Prudencio et al., 2015); and (ii) undergoing repeat associated non-ATG (RAN) translation to produce toxic c9RAN dipeptide repeats (DPRs) in cellular (Almeida et al., 2013; Taylor et al., 2016; Zu et al., 2013), mouse (Chew et al., 2015; O□Rourke et al., 2015), and *Drosophila* (Mizielinska et al., 2014) models.

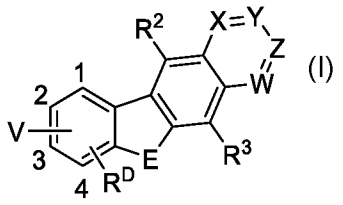
[0003] Current efforts towards developing c9ALS/FTD therapeutics include both antisense oligonucleotides (ASOs) and small molecules that target $r(G_4C_2)^{exp}$. For example, an ASO directed at *C9ORF72* mRNA improved ALS-associated defects in mouse models (Gendron et al., 2017; Jiang et al., 2016). In addition, a small molecule **1a** binds $r(G_4C_2)^{exp}$ and inhibits RAN translation and foci formation in both cultured cells and induced neurons, (Su et al., 2014):



1a

SUMMARY

[0004] Provided herein are compounds or pharmaceutically acceptable salts thereof, having a structure of Formula (I) and their use, e.g., in a method of treating a subject suffering from a disease or condition characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$):



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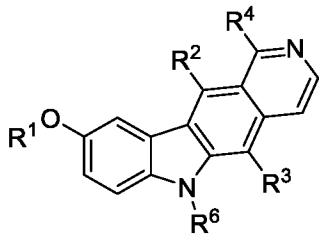
wherein one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4; E is NR^6, O, or S; V is H, halo, OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B; R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkylene-C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or C(O)-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C; R^A and R^B are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{1-6}alkoxy, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-$N(R^N)R^N$, C_{1-6}alkylene-$C(O)NR^NR^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1

or 2 R^C groups; or R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent; each R^N is independently H or C_{1-4}alkyl; each R^C is independently halo, OH, oxo, NR^NR^N, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo; with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then (i) X is CH and OR^1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR^1 is not at the 2-position. In some cases, one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4; E is NR^6, O, or S; V is OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B; R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkylene-C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or C(O)-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C; R^A and R^B are independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-$N(R^N)R^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; or R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and

S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent; each R^N is independently H or C_{1-4}alkyl; each R^C is independently halo, OH, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and

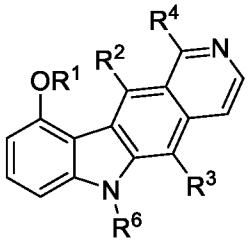
R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo; with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then (i) X is CH and OR^1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR^1 is not at the 2-position.

[0005] Also provided are compounds, or pharmaceutically acceptable salts thereof, of Formula (Xa):

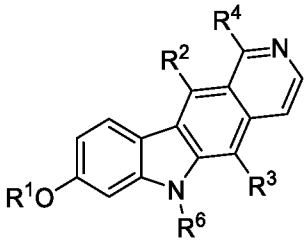


(Xa), wherein R^1 is H, C_{1-6}alkyl, C_{1-6}alkylene-$C(O)C_{1-6}$alkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), or C(O)-(3- to 14-membered heterocyclyl), wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S; and the heterocyclyl is optionally substituted with 1 or 2 R^C groups; R^A and R^B are independently selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $S(O)_{0-2}$-C_{1-6}alkyl, $S(O)_{0-2}$-aryl, $C(O)C_{1-6}$alkyl, $C(O)C_{3-14}$carbocyclyl, C_{3-14}carbocyclyl, C_{1-6}alkylene-C_{3-14}carbocyclyl, aryl, 3- to 14-membered heterocyclyl, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), and 5- to 10-membered heteroaryl, and wherein 1-4 heteroaryl or 1-4 heterocyclyl ring atoms are independently selected from N, O, and S, and the carbocyclyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 R^C groups; each R^C is independently halo, OH, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, $C(O)OC_{1-6}$alkyl, C_{1-6}alkyl, 3- to 14-membered heterocyclyl, and wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S; R^4 is H, C_{1-6}alkyl, NR^AR^B, $C(O)OC_{1-6}$alkyl, $C(O)NR^A$-C_{1-6}alkylene-NR^AR^B, or $C(O)NR^A$–C_{1-6}alkylene-OR^B; R^2 and R^3 are each independently H or CH_3; and R^6 is H or CH_3.

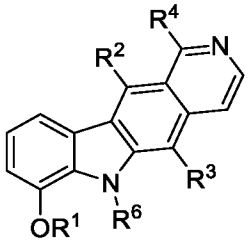
[0006] Also provided are compounds, or pharmaceutically acceptable salts thereof, of Formulae Xb, Xc, and Xd:



(Xb),



(Xc),



(Xd).

[0007] The disclosure also provides as another embodiment is a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier or excipient.

[0008] In accordance with still a further embodiment, optionally in combination with any other embodiment, the disclosure provides any compound as described herein or a pharmaceutically acceptable salt thereof, for use in a method of treating a subject suffering from a disease or condition characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$).

[0009] An additional embodiment is a method for determining whether a test compound selectively inhibits repeat associated non-ATG (RAN) translation. The method comprises the steps of (a) contacting a test cell that expresses $(G_4C_2)_n$-NoATG-[Marker1] and ATG-[Marker2] with the test compound, wherein Marker1 and Marker2 are not the same marker, and wherein *n* is an integer from 5 to 1000 (inclusive); (b) measuring the amounts of Marker1 and Marker2 in the test cell of (a); and (c) comparing the amounts measured in (b), wherein a lower amount of Marker1 compared to Marker2 correlates to a determination that the test compound is a selective inhibitor of (RAN) translation.

DETAILED DESCRIPTION

[0010] Provided herein are nucleic acid-binding compounds that target a nucleotide repeat in a subject, e.g., compounds that target $r(G_4C_2)^{exp}$. These compounds are useful in the treatment of a variety of diseases and disorders, including but not limited to, Amyotrophic Lateral Sclerosis (ALS) or Frontotemporal Dementia, e.g., c9ALS/FTD.

Definitions

[0011] "Alkyl" refers to straight, branched chain, or cyclic hydrocarbyl groups, e.g., “cycloalkyl,” including from 1 to about 20 carbon atoms. For instance, an alkyl can have from 1 to 10 carbon atoms or 1 to 6 carbon atoms. Exemplary alkyl includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, and the like, and also includes branched chain isomers of straight chain alkyl groups, for example without limitation, $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH3)_2$, $C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, and the like. Thus, alkyl groups include primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. An “alkylene” group refers to an alkyl group that is further substituted.

[0012] Each of the terms “halogen,” “halide,” and “halo” refers to -F, -Cl, -Br, or -I. A “haloalkyl” is an alkyl group substituted with one or more halogen.

[0013] The term “alkenyl” refers to straight or branched chain groups from 2 to about 20 carbon atoms having 1-3, 1-2, or at least one carbon to carbon double bond.

[0014] “Alkynyl” refers to a straight or branched chain unsaturated hydrocarbon having the indicated number of carbon atoms and at least one triple bond. Examples of a (C_2-C_8)alkynyl group include, but are not limited to, acetylene, propyne, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne, 1-hexyne, 2-hexyne, 3-hexyne, 1-heptyne, 2-heptyne, 3-heptyne, 1-octyne, 2-octyne, 3-octyne and 4-octyne.

[0015] The term “alkoxy” refers to an -O-alkyl group having the indicated number of carbon atoms. For example, a (C_1-C_6)alkoxy group includes -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-butyl, -O-*sec*-butyl, -O-*tert*-butyl, -O-pentyl, -O-isopentyl, -O-neopentyl, -O-hexyl, -O-isohexyl, and -O-neohexyl.

[0016] The term “carbocyclyl” refers to a monocyclic, bicyclic, tricyclic, or polycyclic, 3- to 14-membered ring system, which is either saturated, such as “cycloalkyl,” or unsaturated, such as “cycloalkenyl.” The carbocyclyl may be attached via any atom. Carbocyclyl, for instance, also contemplates fused rings wherein, for instance, a carbocyclyl is fused to an aryl or heteroaryl ring as defined herein. Representative examples of carbocyclyl include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, phenyl, naphthyl, anthracyl, benzofuranyl, and benzothiophenyl. A carbocyclyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0017] "Aryl" when used alone or as part of another term means a carbocyclic aromatic group whether or not fused having the number of carbon atoms designated or if no number is designated, up to 14 carbon atoms, such as a C_6-C_{14}-aryl. Particular aryl groups are phenyl, naphthyl, biphenyl, phenanthrenyl, naphthacenyl, and the like (see e.g. *Lang's Handbook of Chemistry* (Dean, J. A., ed) 13th ed. Table 7-2 [1985]). A particular aryl is phenyl. "Aryl" also includes aromatic ring systems that are optionally fused with a carbocyclyl ring, as herein defined. An aryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0018] The term "heteroatom" refers to N, O, and S. Inventive compounds that contain N or S atoms can be optionally oxidized to the corresponding N-oxide, sulfoxide, or sulfone compounds.

[0019] "Heteroaryl," alone or in combination with any other moiety described herein, refers to a monocyclic aromatic ring structure containing 5 to 10, such as 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing one or more, such as 1-4, 1-3, or 1-2, heteroatoms independently selected from the group consisting of O, S, and N. Heteroaryl is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. A carbon or heteroatom is the point of attachment of the heteroaryl ring structure such that a stable compound is produced. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrazinyl, quinaoxalyl, indolizinyl, benzo[b]thienyl, quinazolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, pyrazolyl, oxazolyl, thiazolyl, thienyl, isoxazolyl, oxathiadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazolyl, furanyl, benzofuryl, and indolyl. A heteroaryl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0020] "Heterocyclyl" means a saturated or unsaturated non-aromatic monocyclic, bicyclic, tricyclic or polycyclic ring system that has from 3 to 14, such as 3 to 6, atoms in which from 1 to 3 carbon atoms in the ring are replaced by heteroatoms of O, S or N. A heterocyclyl is optionally fused with aryl or heteroaryl of 5-6 ring members, and includes oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of a tertiary ring nitrogen. The point of attachment of the heterocyclyl ring is at a carbon or heteroatom such that a stable ring is retained. Examples of heterocyclyl groups include without limitation morpholino, tetrahydrofuranyl, dihydropyridinyl, piperidinyl, pyrrolidinyl, piperazinyl, dihydrobenzofuryl, dihydroimidazolyl, and dihydroindolyl. A hetercycloalkyl group can be unsubstituted or optionally substituted with one or more substituents as described herein below.

[0021] The term "nitrile" or "cyano" can be used interchangeably and refer to a -CN group. The term "cyanoalkyl" refers to an alkyl group substituted with a cyano group.

[0022] A “hydroxyl” or “hydroxy” refers to an –OH group. The term “hydroxyalkyl” refers to an alkyl group substituted with a hydroxy group.

[0023] An “oxo” refers to a =O group.

[0024] The compounds disclosed herein include isotopically-labeled compounds wherein one or more atoms of the compounds disclosed herein are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature, examples of which include isotopes of hydrogen, such as ^{2}H and ^{3}H, isotopes of carbon, such as ^{11}C and ^{13}C, and isotopes of fluorine, such as ^{18}F. Unless otherwise specifically indicated, an “H” substituent refers to any isotope of hydrogen, ^{1}H, ^{2}H, or ^{3}H. In some cases, one or more hydrogen atoms of the compounds disclosed herein are specifically ^{2}H (“D” or deuterium). Isotopically-labeled compounds as disclosed herein can be prepared by techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and schemes using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

[0025] Compounds described herein can exist in various isomeric forms, including configurational, geometric, and conformational isomers, including, for example, cis- or trans-conformations. The compounds may also exist in one or more tautomeric forms, including both single tautomers and mixtures of tautomers. The term “isomer” is intended to encompass all isomeric forms of a compound of this disclosure, including tautomeric forms of the compound. The compounds of the present disclosure may also exist in open-chain or cyclized forms. In some cases, one or more of the cyclized forms may result from the loss of water. The specific composition of the open-chain and cyclized forms may be dependent on how the compound is isolated, stored or administered. For example, the compound may exist primarily in an open-chained form under acidic conditions but cyclize under neutral conditions. All forms are included in the disclosure.

[0026] Some compounds described herein can have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. A compound of the invention can be in the form of an optical isomer or a diastereomer. Accordingly, the disclosure encompasses compounds and their uses as described herein in the form of their optical isomers, diastereoisomers and mixtures thereof, including a racemic mixture. Optical isomers of the compounds of the disclosure can be obtained by known techniques such as asymmetric synthesis, chiral chromatography, simulated moving bed technology or via chemical separation of stereoisomers through the employment of optically active resolving agents.

[0027] Unless otherwise indicated, the term “stereoisomer” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. Thus, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, for example greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, or greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound, or greater than about 99% by weight of one stereoisomer of the compound and less than about 1% by weight of the other stereoisomers of the compound. The stereoisomer as described above can be viewed as composition comprising two stereoisomers that are present in their respective weight percentages described herein.

[0028] If there is a discrepancy between a depicted structure and a name given to that structure, then the depicted structure controls. Additionally, if the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. In some cases, however, where more than one chiral center exists, the structures and names may be represented as single enantiomers to help describe the relative stereochemistry. Those skilled in the art of organic synthesis will know if the compounds are prepared as single enantiomers from the methods used to prepare them.

[0029] As used herein, and unless otherwise specified, the term “compound” is inclusive in that it encompasses a compound or a pharmaceutically acceptable salt, stereoisomer, and/or tautomer thereof. Thus, for instance, a compound of Formula I includes a pharmaceutically acceptable salt of a tautomer of the compound.

[0030] In this description, a “pharmaceutically acceptable salt” is a pharmaceutically acceptable, organic or inorganic acid or base salt of a compound of the invention. Representative pharmaceutically acceptable salts include, e.g., alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate,

estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosaliculate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts. A pharmaceutically acceptable salt can have more than one charged atom in its structure. In this instance the pharmaceutically acceptable salt can have multiple counterions. Thus, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counterions.

[0031] The terms “treat”, “treating” and “treatment” refer to the amelioration or eradication of a disease or symptoms associated with a disease. In certain embodiments, such terms refer to minimizing the spread or worsening of the disease resulting from the administration of one or more prophylactic or therapeutic agents to a patient with such a disease.

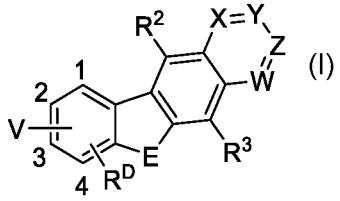
[0032] The terms “prevent,” “preventing,” and “prevention” refer to the prevention of the onset, recurrence, or spread of the disease in a patient resulting from the administration of a prophylactic or therapeutic agent.

[0033] The term “effective amount” refers to an amount of a compound of the invention or other active ingredient sufficient to provide a therapeutic or prophylactic benefit in the treatment or prevention of a disease or to delay or minimize symptoms associated with a disease. Further, a therapeutically effective amount with respect to a compound of the invention means that amount of therapeutic agent alone, or in combination with other therapies, that provides a therapeutic benefit in the treatment or prevention of a disease. Used in connection with a compound of the invention, the term can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of disease, or enhances the therapeutic efficacy of or synergies with another therapeutic agent.

[0034] A “patient” or “subject” includes an animal, such as a human, cow, horse, sheep, lamb, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig. In accordance with some embodiments, the animal is a mammal such as a non-primate and a primate (e.g., monkey and human). In one embodiment, a patient is a human, such as a human infant, child, adolescent or adult.

COMPOUNDS

[0035] As described generally above, the present disclosure provides compounds and pharmaceutically acceptable salts thereof, wherein the compounds conform to formula I:



(I)

wherein

one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4;

E is NR^6, O, or S;

V is H, halo, OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B;

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkylene-C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or $C(O)$-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C;

R^A and R^B are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{1-6}alkoxy, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-

$N(R^N)R^N$, C_{1-6}alkylene-$C(O)NR^NR^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; or

R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent;

each R^N is independently H or C_{1-4}alkyl;

each R^C is independently halo, OH, oxo, NR^NR^N, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and

R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then

(i) X is CH and OR^1 is not OH or OMe; or

(ii) E is not NH or NMe; or

(iii) OR^1 is not at the 2-position. In some cases, one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4; E is NR^6, O, or S; V is OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B; R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkylene-C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or C(O)-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and

S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C; R^A and R^B are independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-$N(R^N)R^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; or R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent; each R^N is independently H or C_{1-4}alkyl; each R^C is independently halo, OH, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo; with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then (i) X is CH and OR^1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR^1 is not at the 2-position.

[0036] In some cases, one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4;

E is NR^6, O, or S;

V is OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B;

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or C(O)-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C;

R^A and R^B are independently H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-$N(R^N)R^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; or

R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent;

each R^N is independently H or C_{1-4}alkyl;

each R^C is independently halo, OH, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and

R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

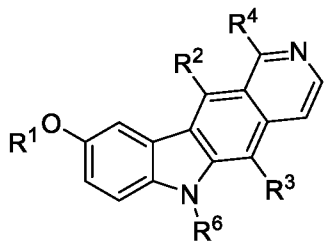
with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then

(i) X is CH and OR^1 is not OH or OMe; or

(ii) E is not NH or NMe; or

(iii) OR^1 is not at the 2-position.

[0037] The present disclosure also provides compounds and pharmaceutically acceptable salts thereof, wherein the compounds conform to Formula (Xa):



(Xa),

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}alkylene-$C(O)C_{1-6}$alkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), or C(O)-(3- to 14-membered heterocyclyl), wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S; and the

heterocyclyl is optionally substituted with 1 or 2 R^C groups;

R^A and R^B are independently selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $S(O)_{0-2}$-C_{1-6}alkyl, $S(O)_{0-2}$-aryl, $C(O)C_{1-6}$alkyl, $C(O)C_{3-14}$carbocyclyl, C_{3-14}carbocyclyl, C_{1-6}alkylene-C_{3-14}carbocyclyl, aryl, 3- to 14-membered heterocyclyl, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), and 5- to 10-membered heteroaryl, and wherein 1-4 heteroaryl or 1-4 heterocyclyl ring atoms are independently selected from N, O, and S, and the carbocyclyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 R^C groups;

each R^C is independently halo, OH, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, $C(O)OC_{1-6}$alkyl, C_{1-6}alkyl, 3- to 14-membered heterocyclyl, and wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S;

R^4 is H, C_{1-6}alkyl, NR^AR^B, $C(O)OC_{1-6}$alkyl, $C(O)NR^A$-C_{1-6}alkylene-NR^AR^B, or $C(O)NR^A$–C_{1-6}alkylene-OR^B;

R^2 and R^3 are each independently H or CH_3; and

R^6 is H or CH_3.

[0038] In some cases, V is at the 1-position. In some cases, V is at the 2-position. In some cases, V is at the 3-position. In some cases, V is at the 4-position. In some cases, V is OR^1 or $C(O)NR^NR^1$. In some cases, V is OR^1. In some cases V is $C(O)NR^NR^1$ or $C(O)R^1$. In some cases, V is $C(O)NR^NR^1$. In some cases, V is NR^ANR^B. In some cases, V is piperazinyl optionally substituted with methyl or optionally comprising a spiro cyclopropyl substituent. In some cases, V is piperazinyl substituted with methyl or optionally comprising a spiro cyclopropyl substituent. In some cases, V is unsubstituted piperazinyl.

[0039] In some cases, R^1 is C_{1-6}alkyl, C_{0-6}alkylene-CO_2R^N, C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkyleneNR^{A}R^B, C_{1-6}alkylene-$C(O)NR^AR^B$, or C_{1-6}alkylene(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S). In some cases, R^1 is C_{1-6}alkyleneNR^{A}R^B. In some cases, R^1 is C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-(N-methylpiperazinyl), C_{1-6}alkylene-morpholinyl, C_{1-6}alkylene-$N(Me)_2$, C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-$N(Et)_2$, C_{1-6}alkylene-pyrrolidinyl, or C_{1-6}alkylene-piperidinyl. In some cases, R^1 is C_{1-6}alkylene-$C(NH)NR^AR^B$. In some cases, R^1 is C_{1-6}alkylene-$C(NH)NH_2$. In some cases, R^1 is C_{1-6}alkylene(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S). In some cases, R^1 is C_{1-6}alkylene-(4,5-dihydro-2-imidazolyl). In some cases, R^1 is C_{1-6}alkylene-$C(O)NR^AR^B$. In some cases, R^1 is C_{1-6}alkylene-$C(O)NH_2$, C_{1-6}alkylene-$C(O)NMe_2$, C_{1-6}alkylene-C(O)NHMe, C_{1-6}alkylene-C(O)-piperazinyl, C_{1-6}alkylene-C(O)-(methylpiperazinyl), C_{1-6}alkylene-$C(O)NHC_{1-6}$alkylene-morpholinyl, C_{1-6}alkylene-$C(O)NHC_{1-6}$alkylene-NH_2, C_{1-6}alkylene-$C(O)NHC_{1-6}$alkylene-NHMe, or C_{1-6}alkylene-$C(O)NHC_{1-6}$alkylene-NMe_2.

[0040] In some cases, E is O. In some cases, E is S. In some cases, E is NR^6.

[0041] In some cases, R^6 is H, C_{1-6}alkyl or C_{1-6}haloalkyl. In some cases, R^6 is C_{1-6}alkyl or C_{1-6}haloalkyl. In some cases, R^6 is H or Me. In some cases, R^6 is H. In some cases, R^6 is Me. In some specific cases, R^6 is CD_3. In some cases, R^6 is C_{1-6}alkylene-NR^AR^B. In some cases, R^6 is C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-(methylpiperazinyl), C_{1-6}alkylene-morpholinyl, C_{1-6}alkylene-$N(Me)_2$, C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-$N(Et)_2$, C_{1-6}alkylene-pyrrolidinyl, or C_{1-6}alkylene-piperidinyl. In some cases, R^6 is C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S). In some cases, R^6 is benzyl, C_{1-6}hydroxyalkylenephenyl, C_{1-6}alkylene-pyridinyl, C_{1-6}alkylene-tetrahydrothiophenedioxide, C_{1-6}alkylene-imidazoyl, C_{1-6}alkylene-(methylimidazolyl), or C_{1-6}alkylene-(4,5-dihydro-2-imidazolyl).

[0042] In some cases, R^2 is H, OH, or C_{1-6}alkyl. In some cases, R^2 is H or C_{1-6}alkyl. In some cases, R^2 is H. In some cases, R^2 is OH. In some cases, R^2 is C_{1-6}alkyl. In some cases, R^2 is methyl. In some specific cases, R^2 is CD_3.

[0043] In some cases, R^3 is H, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl. In some cases, R^3 is H or C_{1-6}alkyl. In some cases, R^3 is H. In some cases, R^3 is C_{1-6}alkyl. In some cases, R^3 is methyl. In some specific cases, R^3 is CD_3. In some cases, R^3 is halo or C_{1-6}haloalkyl. In some cases, R^3 is halo. In some cases, R^3 is C_{1-6}haloalkyl. In some cases, R^3 is F or CF_3. In some cases, R^3 is F. In some cases, R^3 is CF_3.

[0044] In some cases, both R^2 and R^3 are C_{1-6}alkyl. In some cases, both R^2 and R^3 are methyl.

[0045] In some cases, X is N. In some cases, Y is N. In some cases, Z is N. In some cases, W is N.

[0046] In some cases, each of X, Y, Z, and W is CR^4.

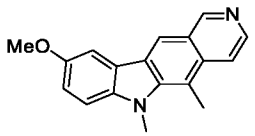
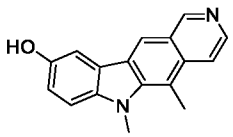
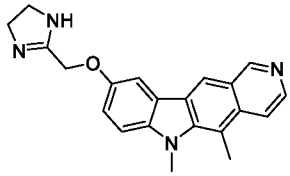
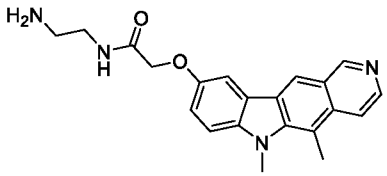
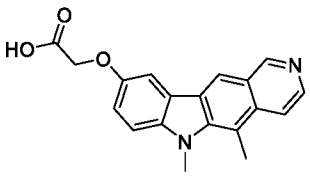
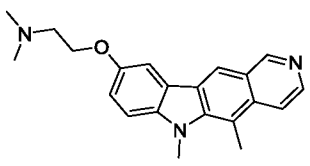
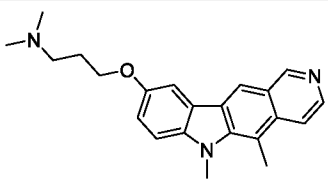
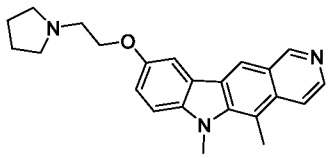
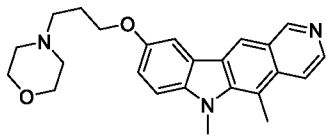
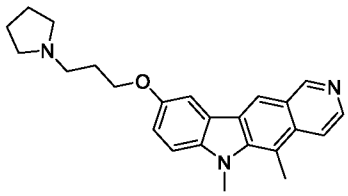
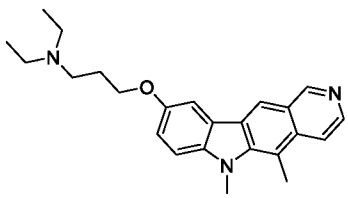
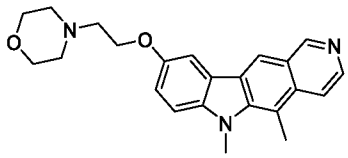
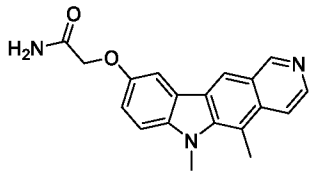
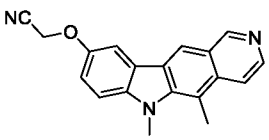
[0047] In some cases, each R^4 is independently H, CO_2H, $C(O)NR^N$-C_1-C_6-alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B. In some cases, each R^4 is H. In some cases, at least one R^4 is $C(O)NHC_{1-6}$alkyleneNMe$_2$ or CO_2H. In some cases, at least one R^4 is $C(O)NHC_{1-6}$alkyleneNMe$_2$. In some cases, at least one R^4 is CO_2H. In some cases, one R^4 is CO_2H, $C(O)NR^N$-C_1-C_6-alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and all other R^4 are H.

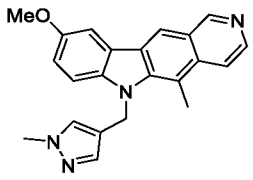
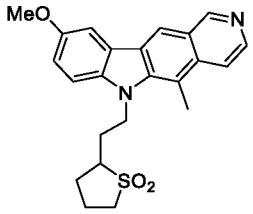
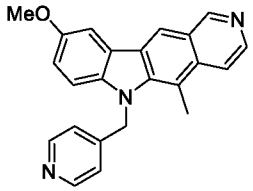
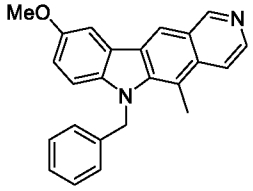
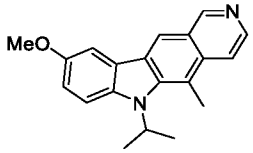
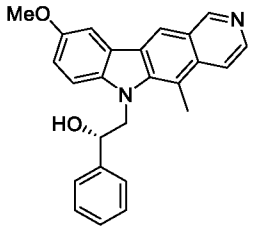
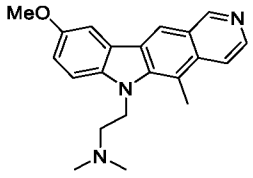
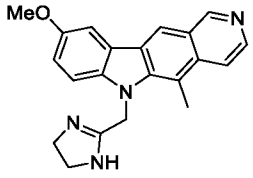
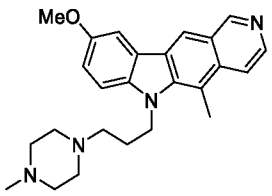
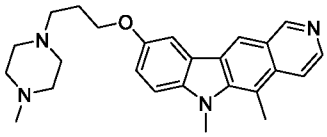
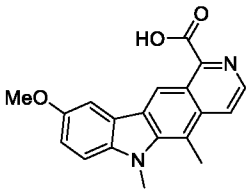
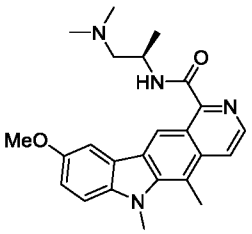
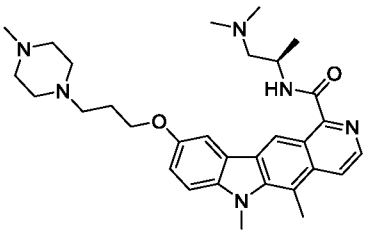
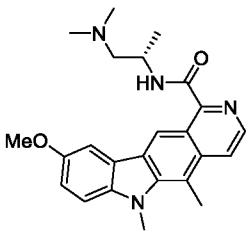
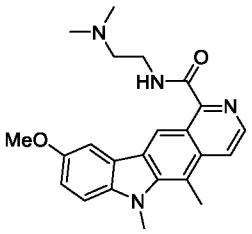
[0048] In some cases, R^D is H or halo. In some cases, R^D is H. In some cases, R^D is halo. In some cases, R^D is F or Cl. In some cases, R^D is F. In some cases, In some cases, R^D is Cl. In some cases, R^D is C_{1-6}alkyl or C_{1-6}haloalkyl. In some cases, R^D is C_{1-6}alkyl. In some

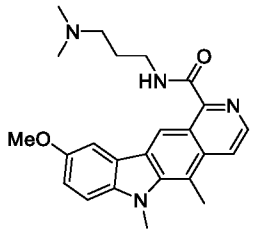
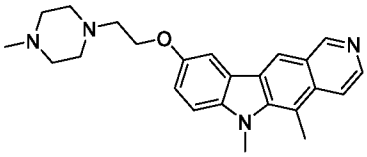
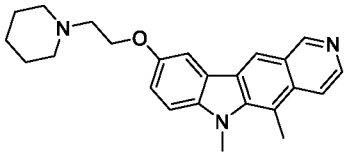
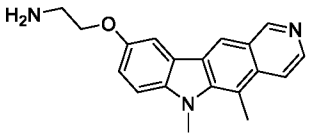
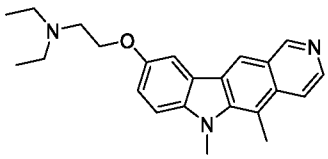
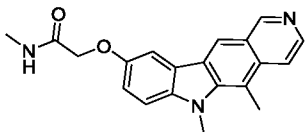
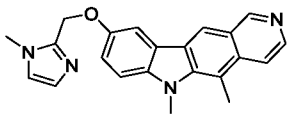
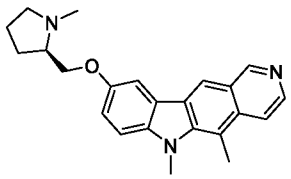
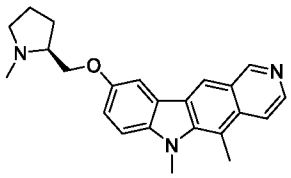
cases, R^D is CH_3. In some cases, R^D is CD_3. In some cases, R^D is C_{1-6}haloalkyl. In some cases, R^D is CF_3.

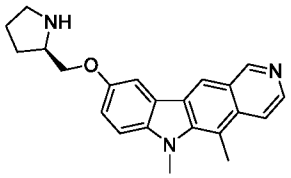
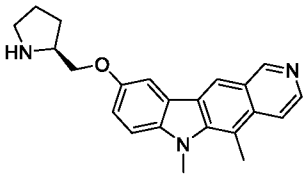
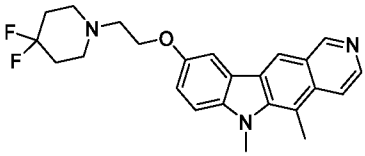
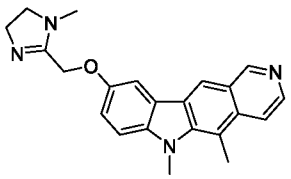
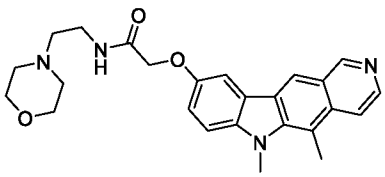
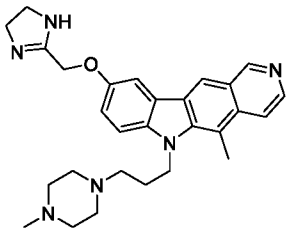
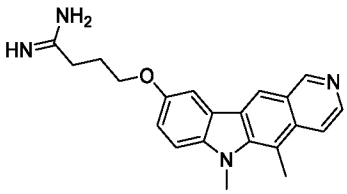
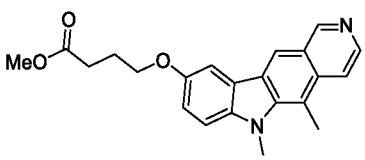
[0049] In various embodiments, the disclosure provides specific examples of Formula I compounds, and their pharmaceutically acceptable salts, as set forth in Table A, Table B, or Table C below:

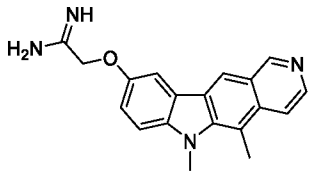
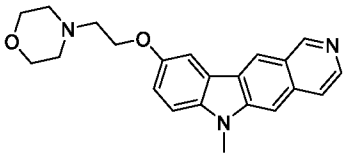
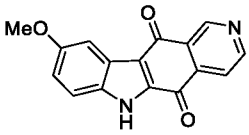
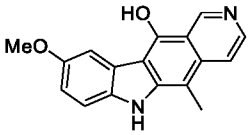
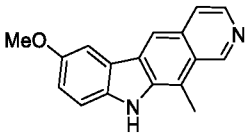
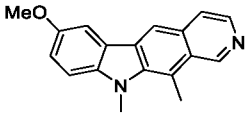
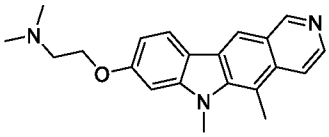
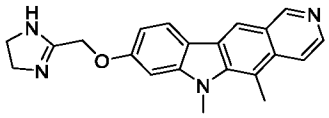
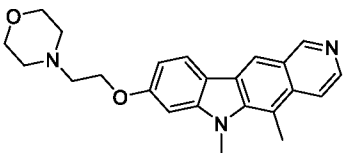
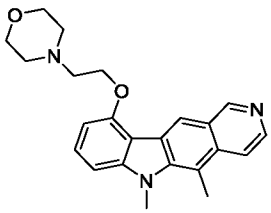
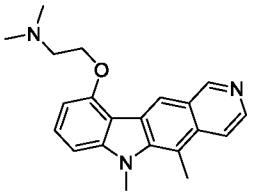
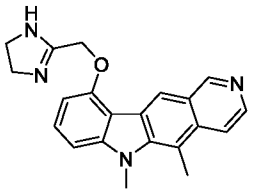
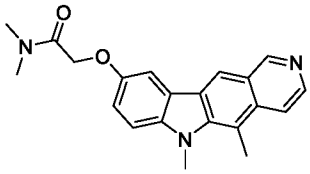
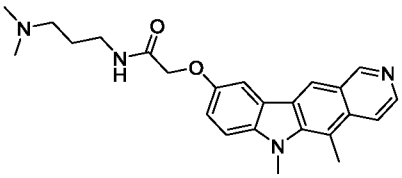
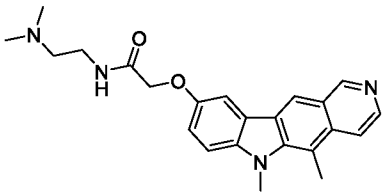
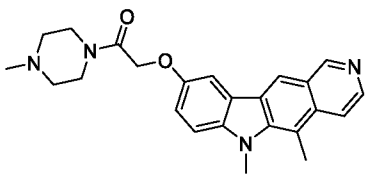
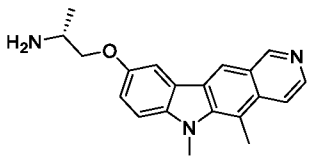
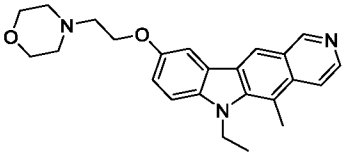
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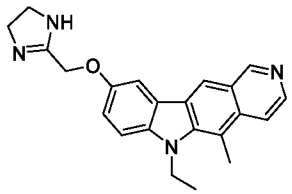
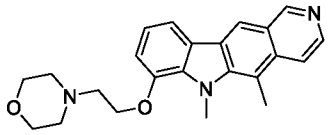
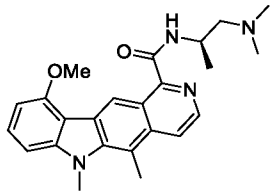
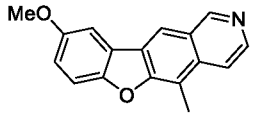
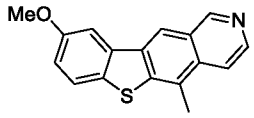
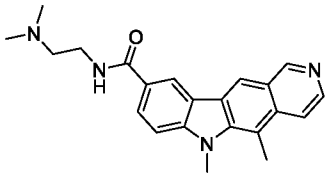
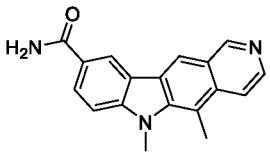
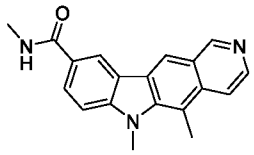
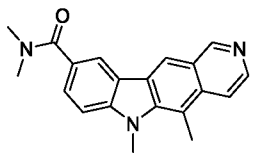
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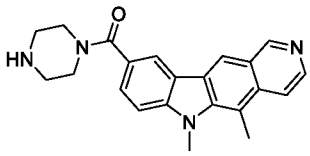
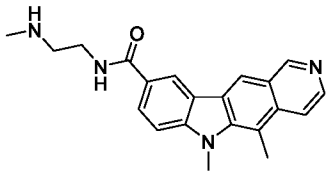
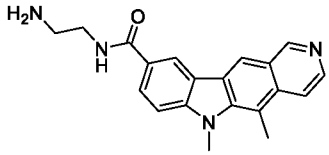
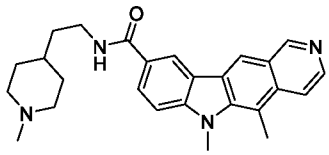
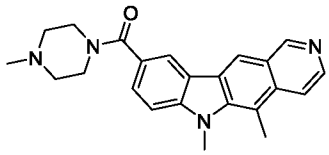
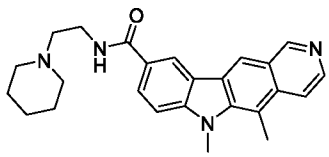
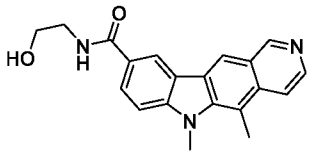
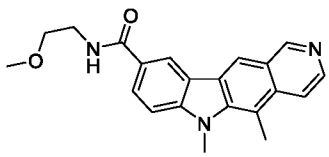
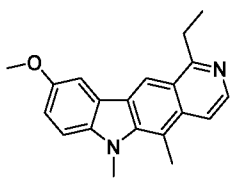
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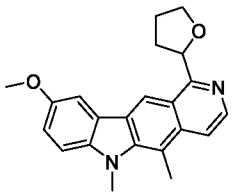
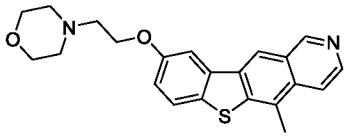
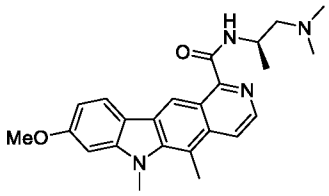
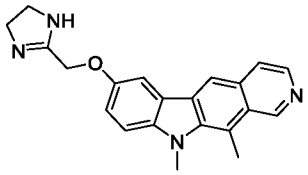
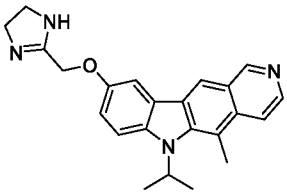
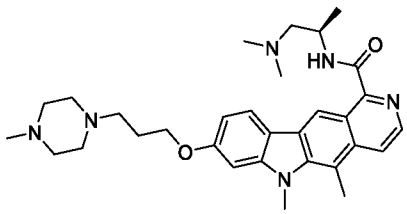
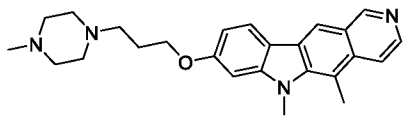
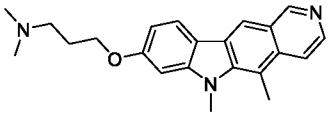
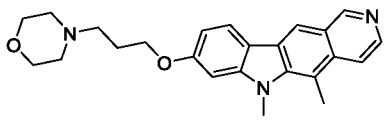
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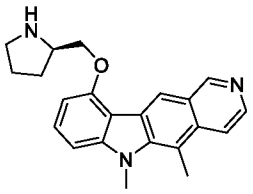
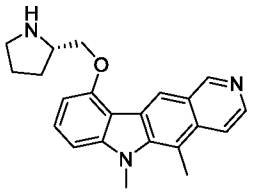
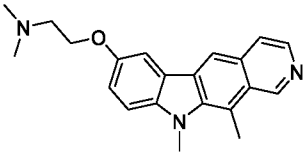
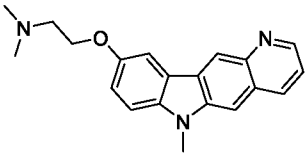
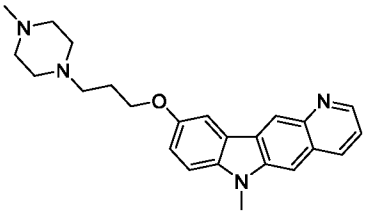
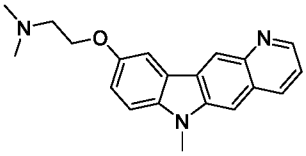
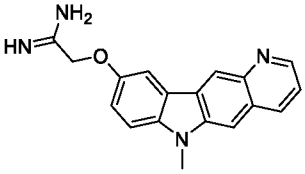
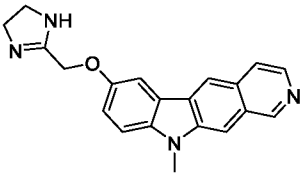
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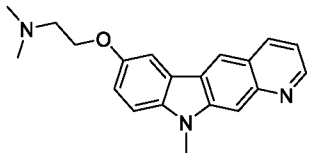
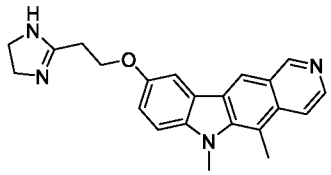
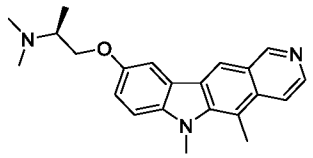
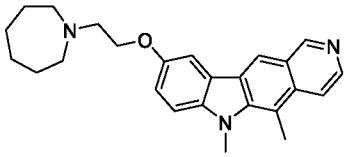
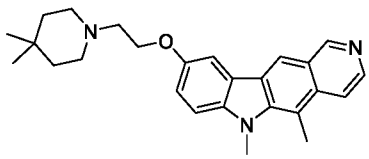
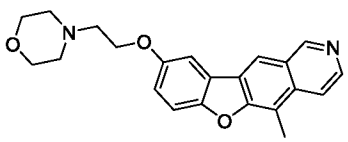
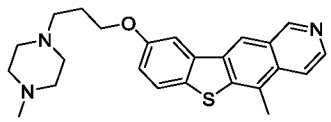
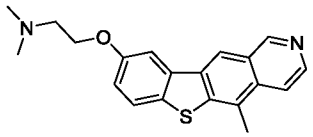
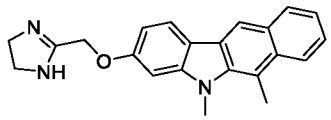
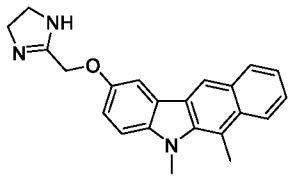
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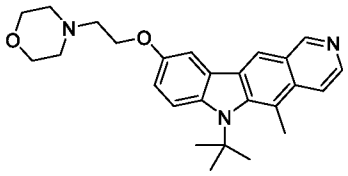
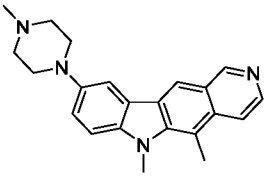
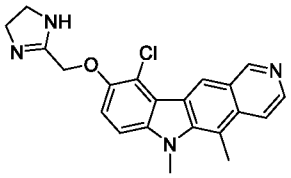
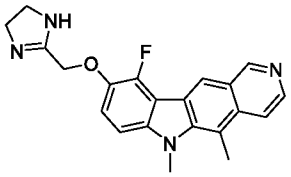
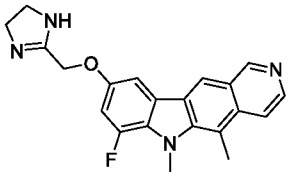
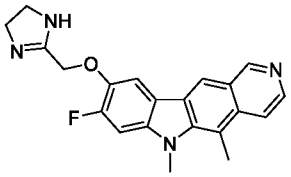
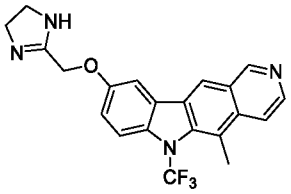
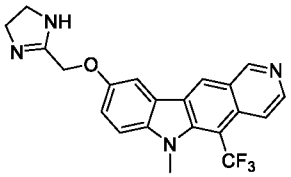
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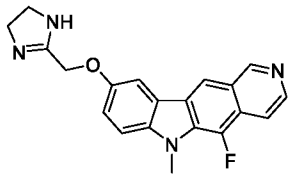
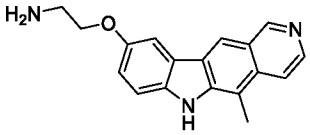
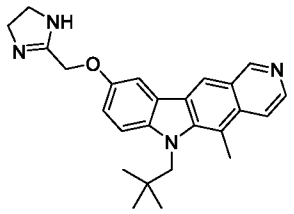
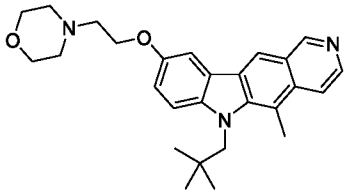
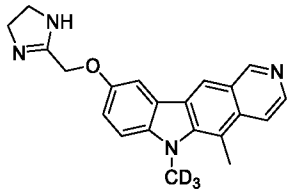
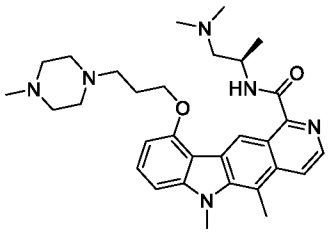
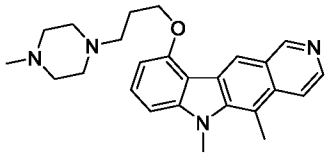
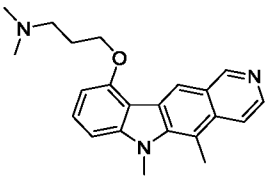
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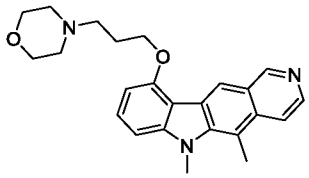
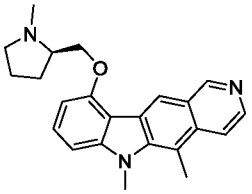
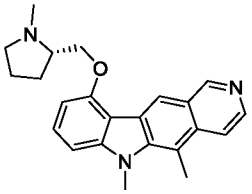
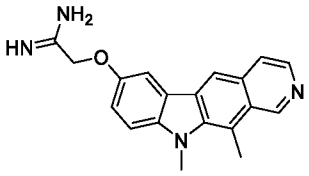
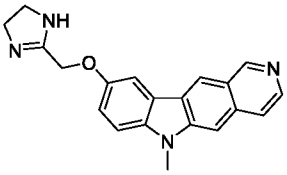
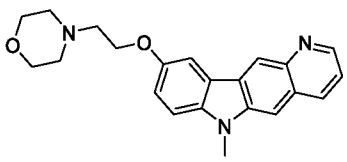
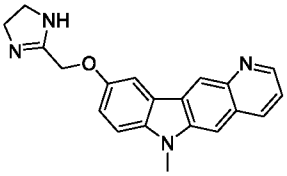
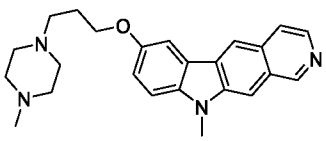
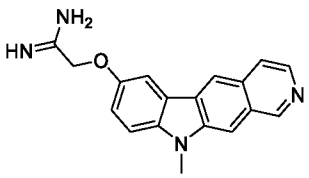
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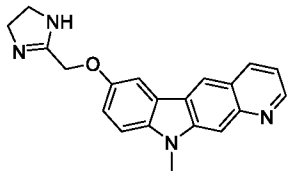
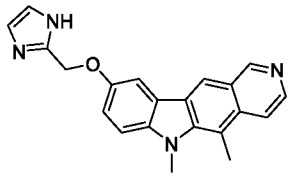
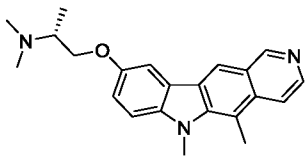
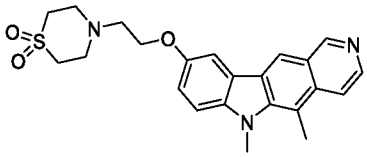
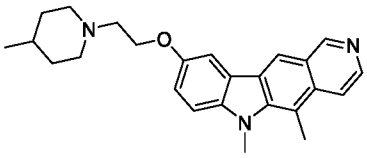
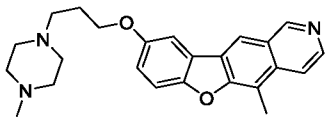
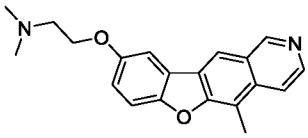
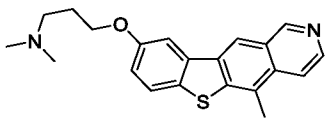
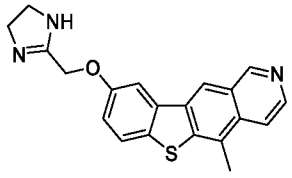
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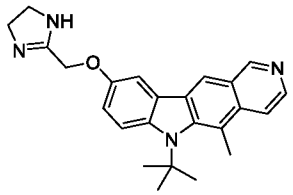
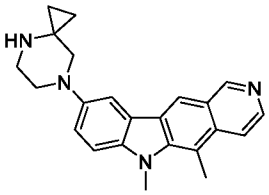
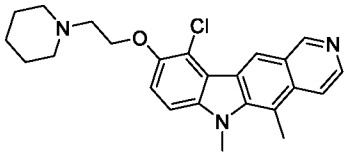
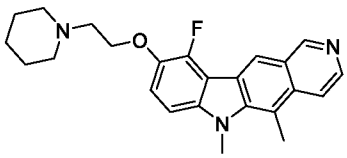
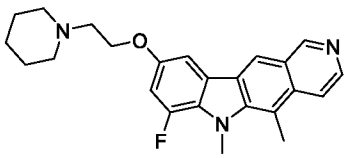
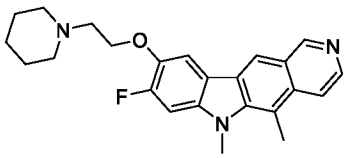
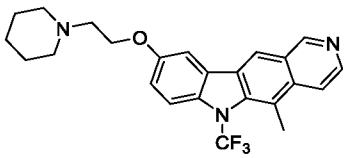
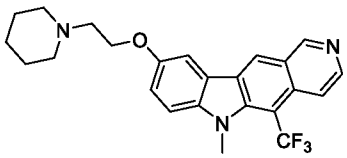
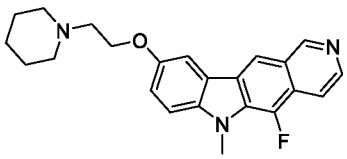
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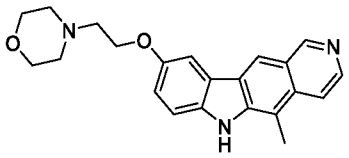
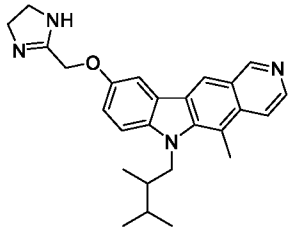
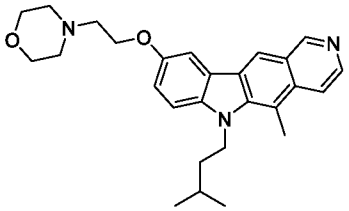
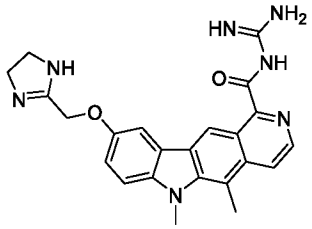
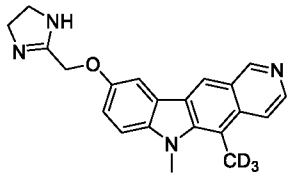
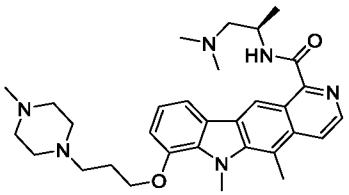
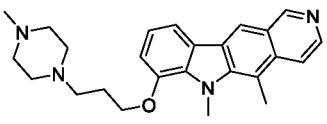
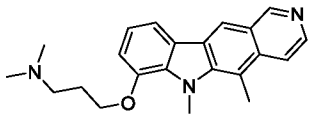
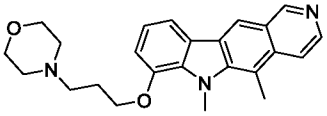
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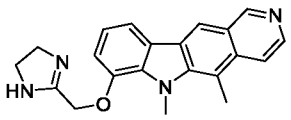
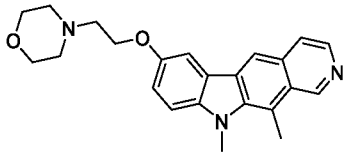
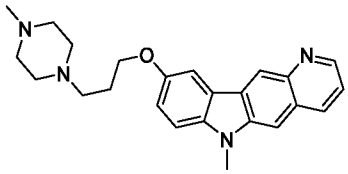
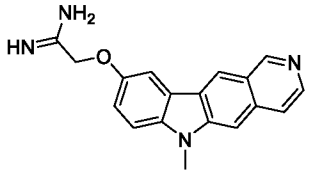
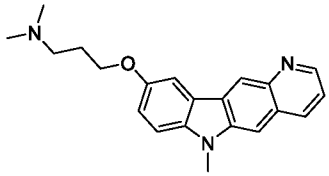
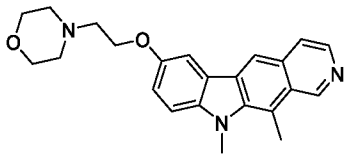
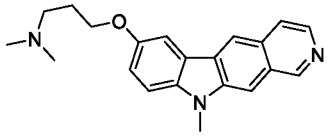
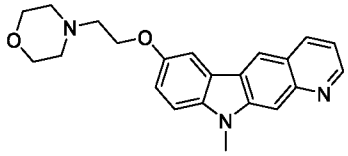
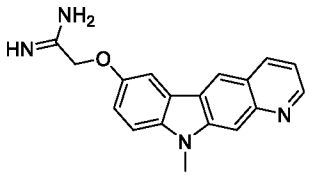
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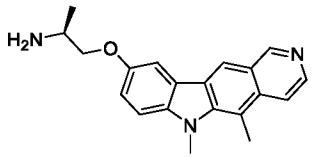
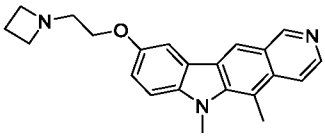
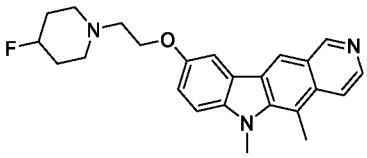
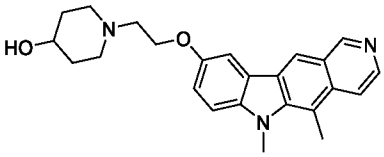
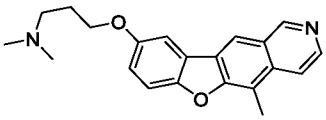
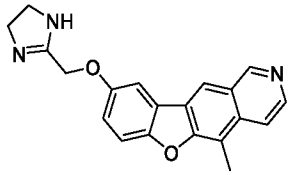
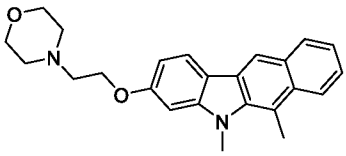
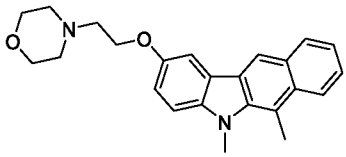
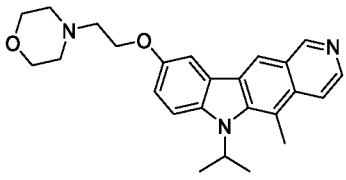
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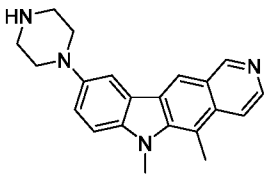
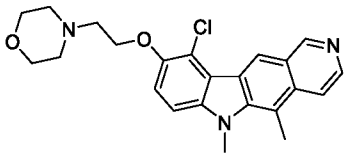
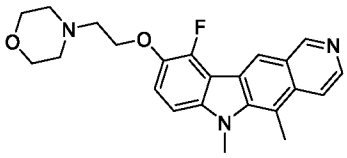
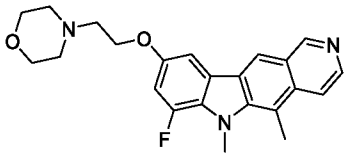
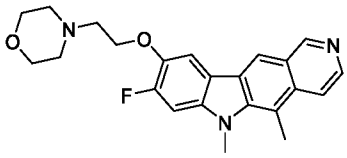
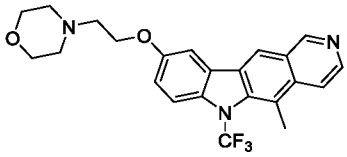
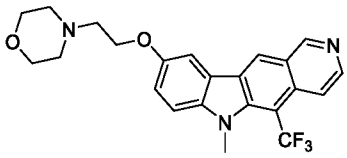
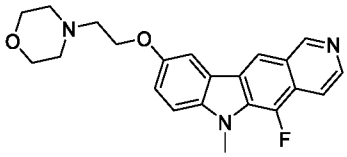
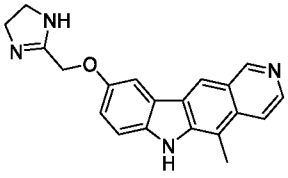
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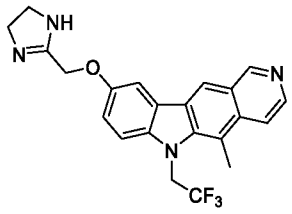
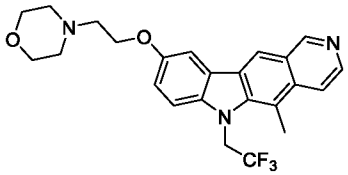
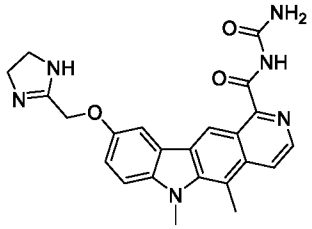
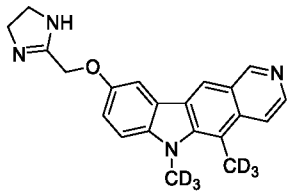
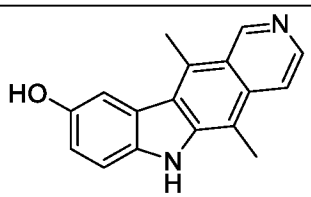
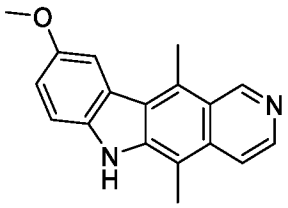
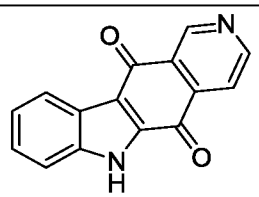
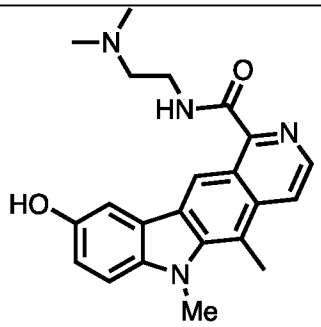
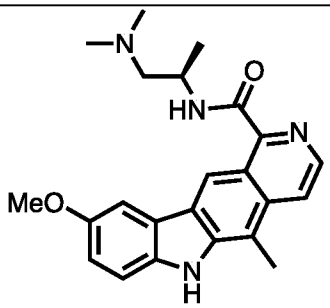
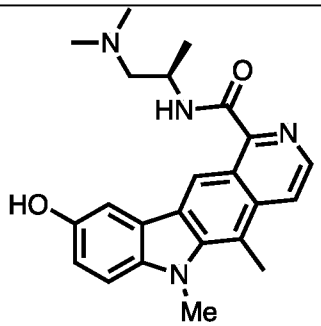
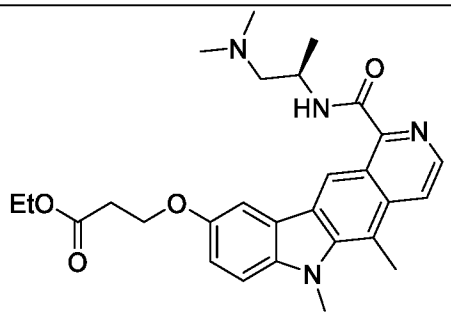
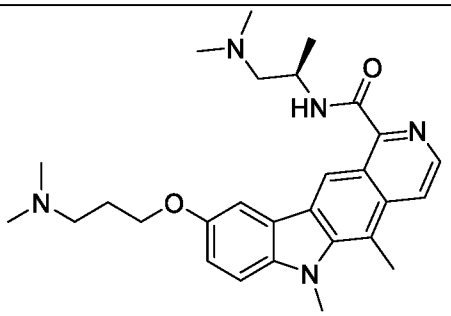
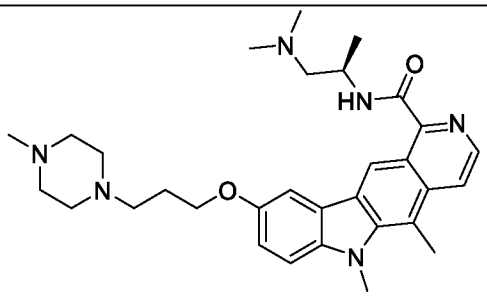
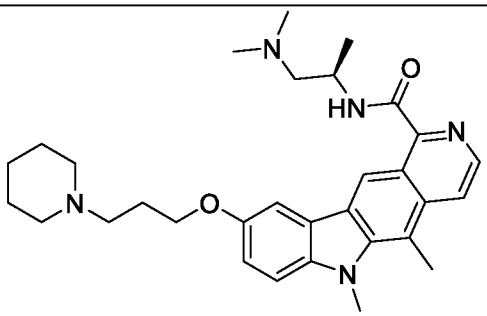
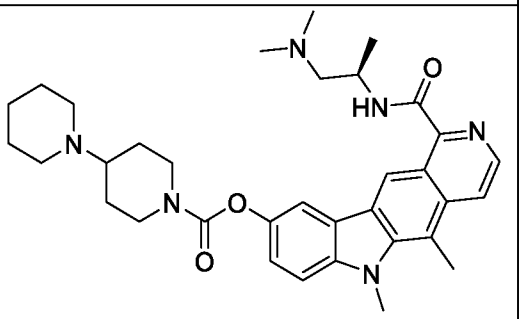
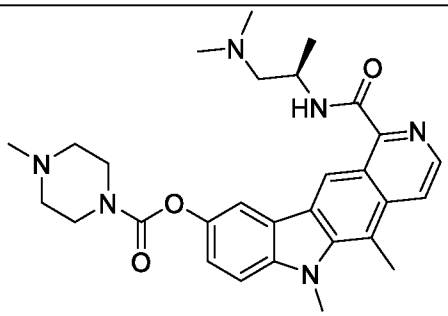
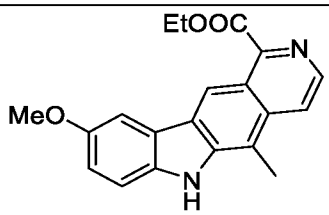
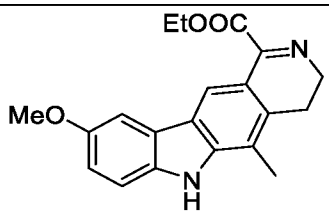
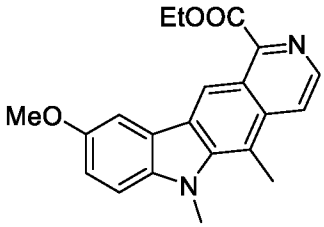
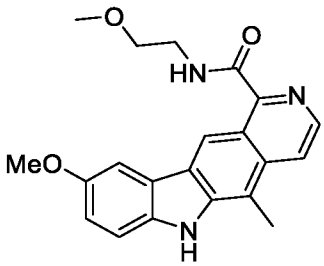
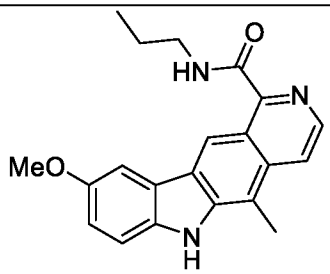
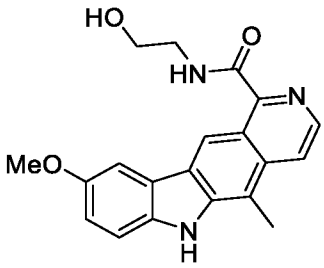
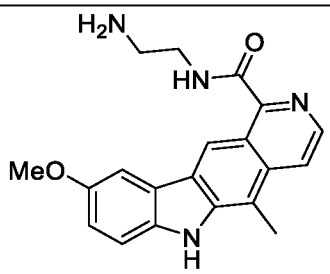
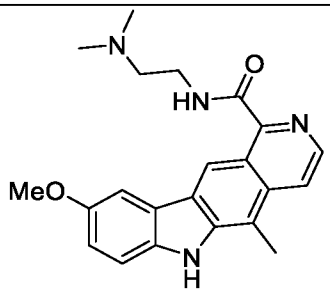
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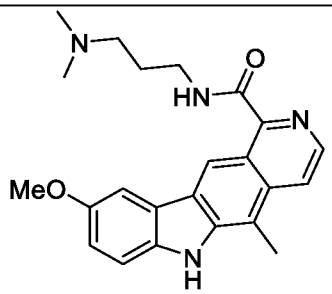
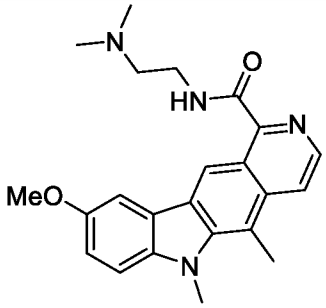
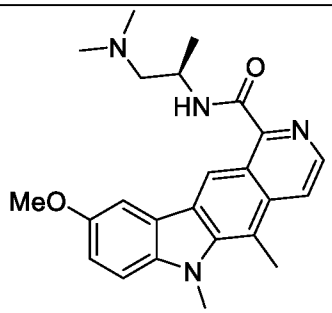
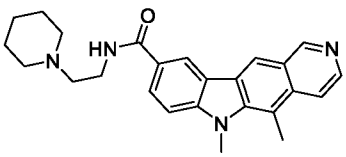
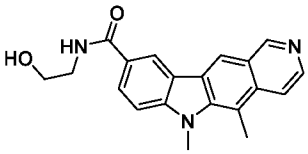
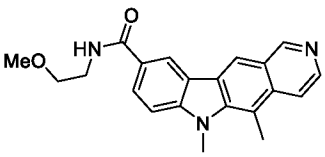
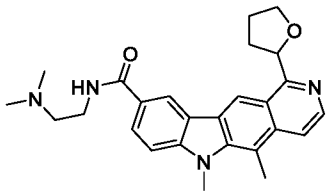
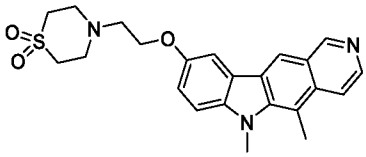
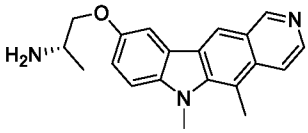
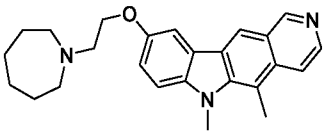
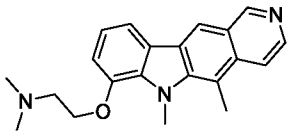
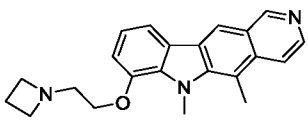
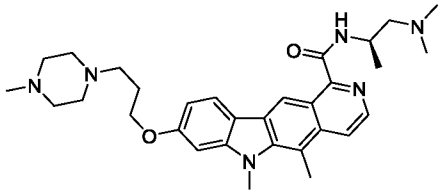
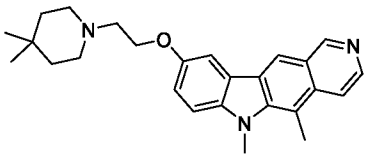
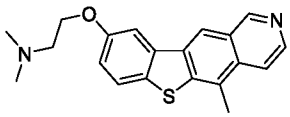
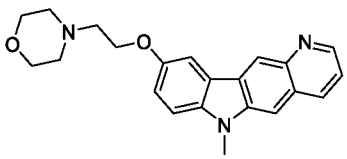
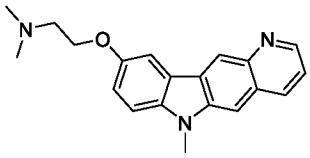
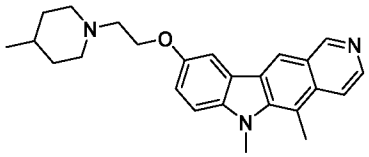
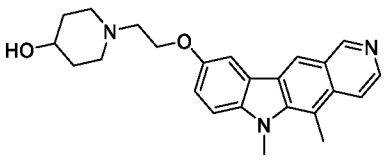
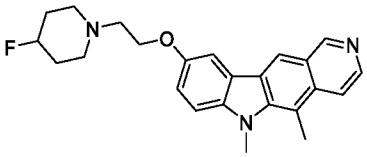
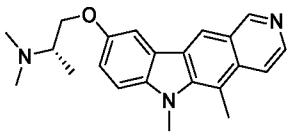
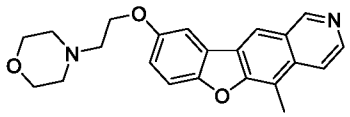
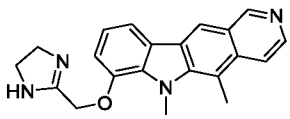
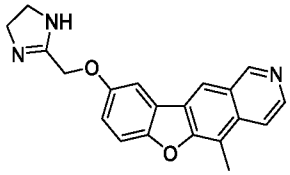
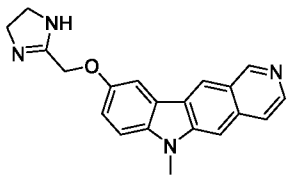
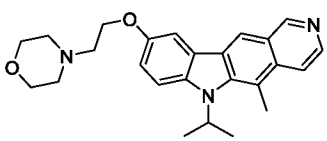
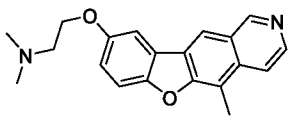
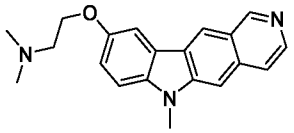
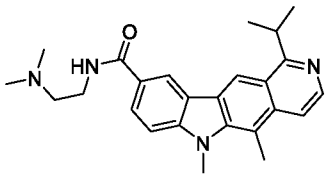
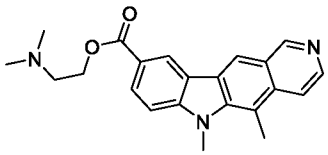
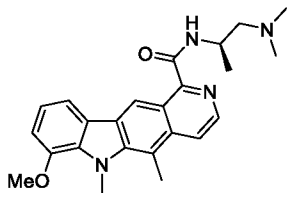
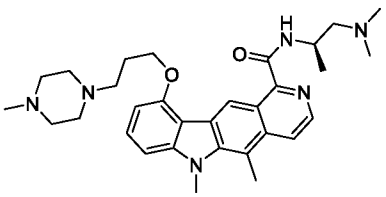
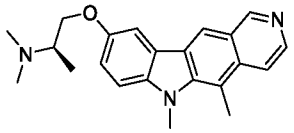
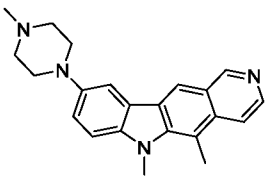
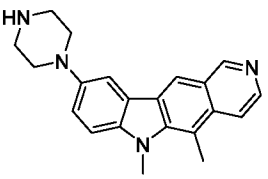
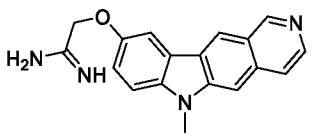
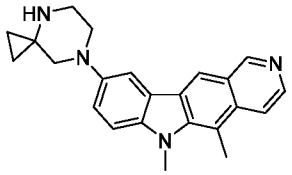
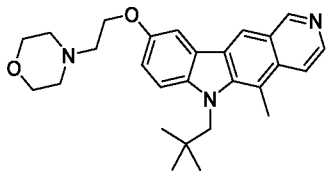
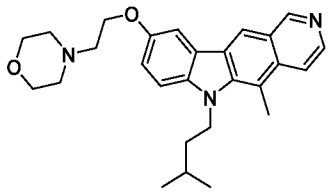
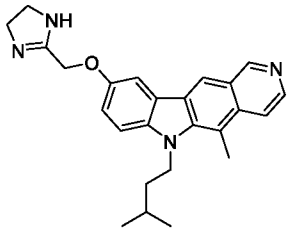
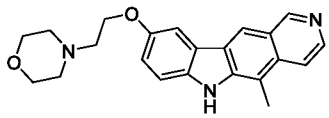
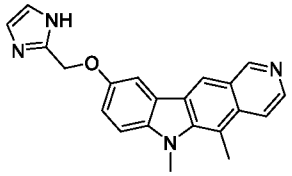
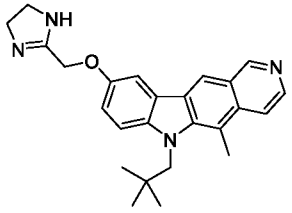
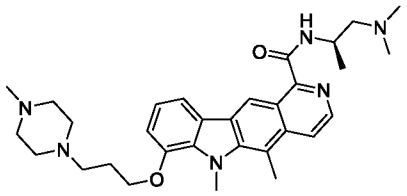
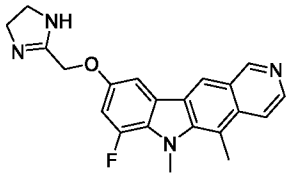
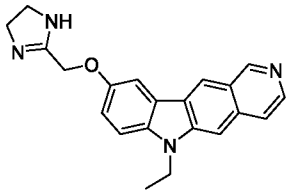
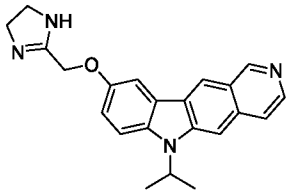
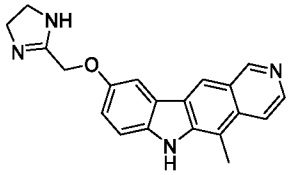
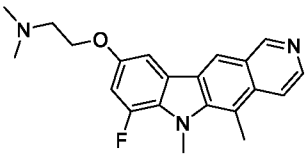
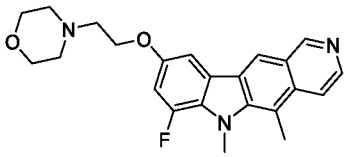
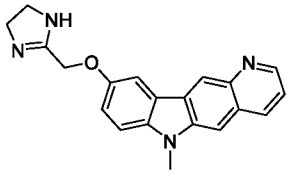
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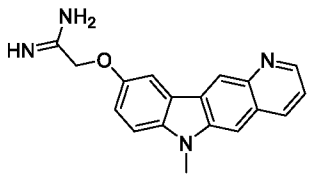
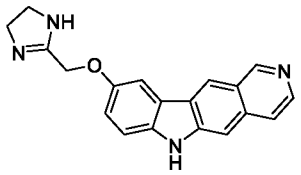
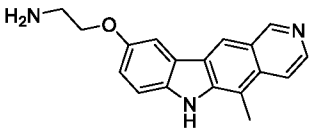
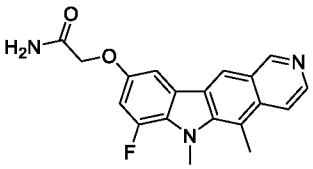
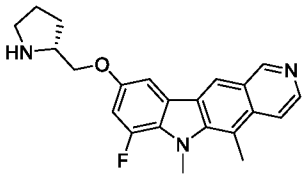
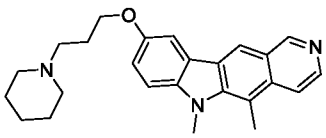
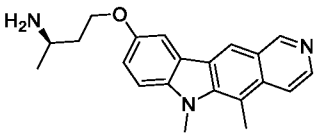
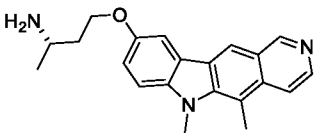
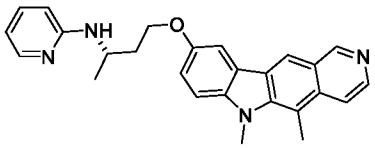
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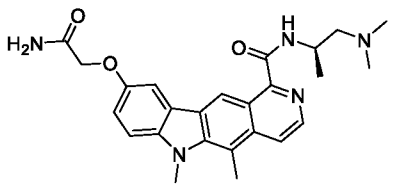
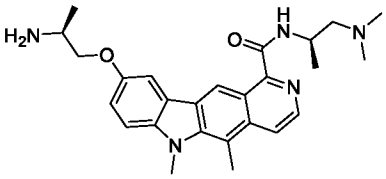
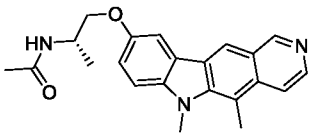
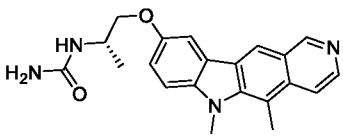
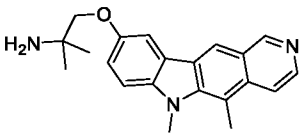
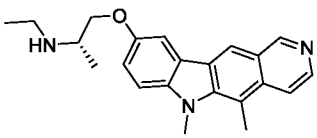
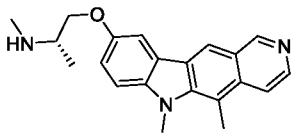
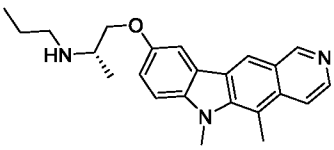
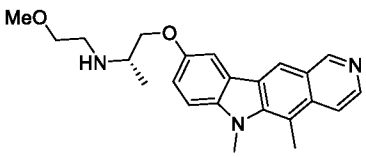
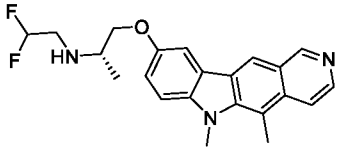
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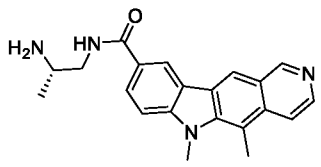
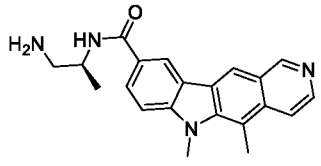
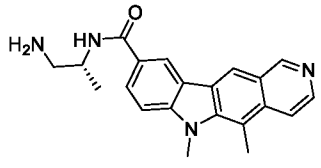
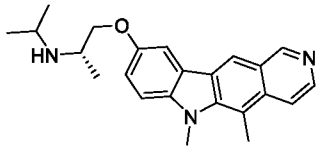
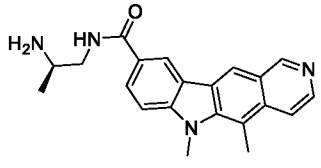
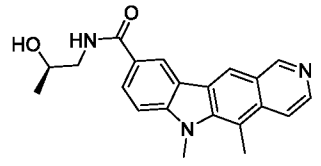
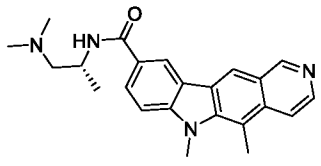
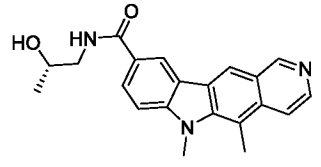
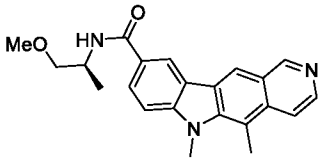
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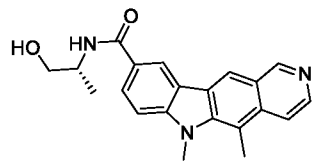
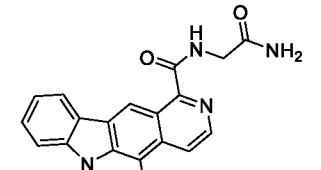
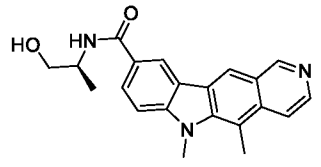
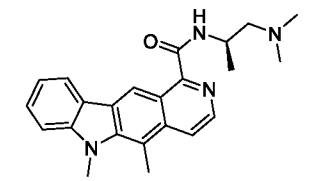
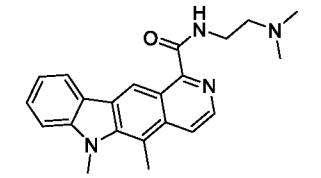
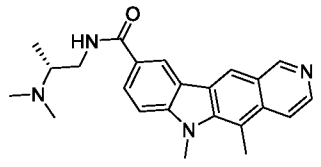
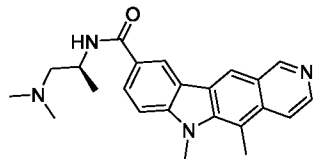
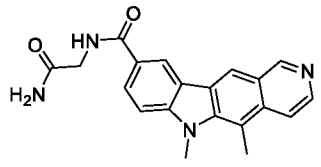
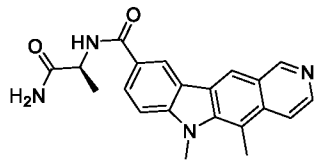
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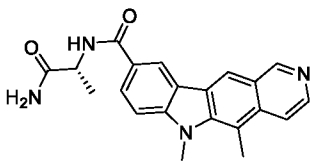
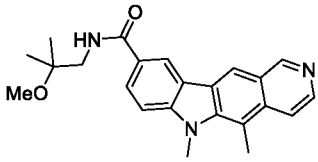
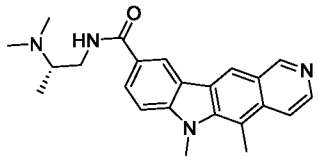
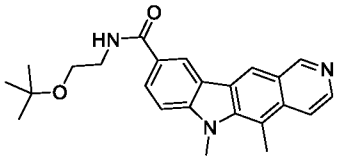
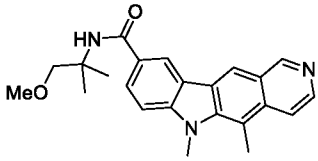
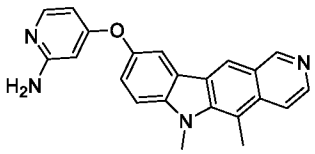
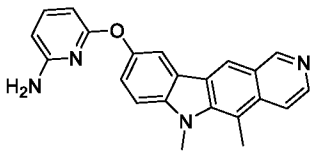
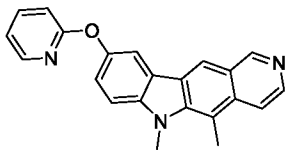
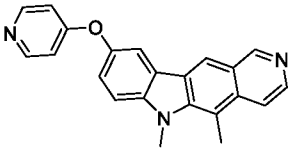
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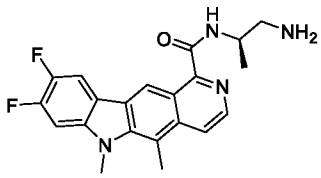
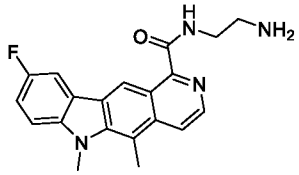
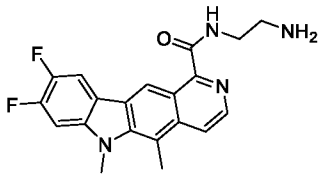
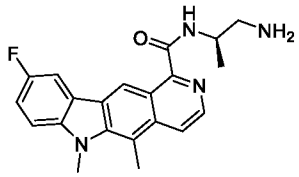
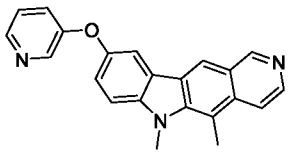
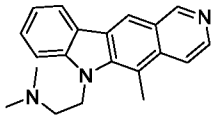
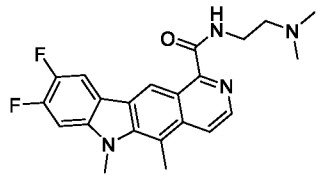
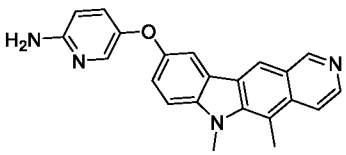
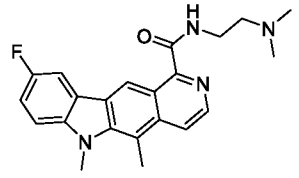
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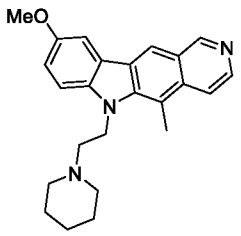
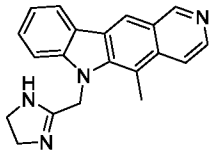
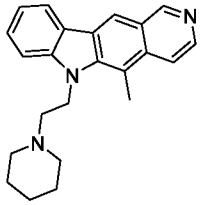
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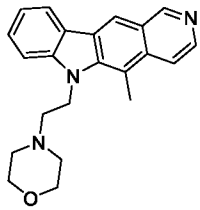
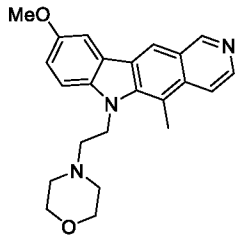
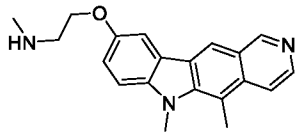
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PHARMACEUTICAL COMPOSITION

[0050] The disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of one or more compounds as disclosed herein or a pharmaceutically acceptable salt, stereoisomer, or tautomer, in admixture with a pharmaceutically acceptable carrier. In some embodiments, the composition further contains, in accordance with accepted practices of pharmaceutical compounding, one or more additional therapeutic agents, pharmaceutically acceptable excipients, diluents, adjuvants, stabilizers, emulsifiers, preservatives, colorants, buffers, flavor imparting agents.

[0051] In some embodiments, the pharmaceutical composition comprises a compound selected from those illustrated in Table A or Table B or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[0052] The pharmaceutical composition of the present disclosure is formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular subject being treated, the clinical condition of the subject, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

[0053] The “therapeutically effective amount” of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) that is administered is governed by such considerations, and is the minimum amount necessary to inhibit expanded G4C2 repeat

RNA (r(G4C2)exp). Such amount may be below the amount that is toxic to normal cells, or the subject as a whole. Generally, the initial therapeutically effective amount of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure that is administered is in the range of about 0.01 to about 200 mg/kg or about 0.1 to about 20 mg/kg of patient body weight per day, with the typical initial range being about 0.3 to about 15 mg/kg/day. Oral unit dosage forms, such as tablets and capsules, may contain from about 1 mg to about 1000 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In some embodiments, such dosage forms contain from about 50 mg to about 500 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In various embodiments, such dosage forms contain from about 25 mg to about 200 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In some embodiments, such dosage forms contain from about 10 mg to about 100 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure. In some embodiments, such dosage forms contain from about 5 mg to about 50 mg of a compound (or a pharmaceutically acceptable salt, stereoisomer, or tautomer thereof) of the present disclosure.

[0054] The disclosed compositions can be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal, and intrathecal injection or infusion techniques.

[0055] Suitable oral compositions in accordance with the invention include without limitation tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, syrups or elixirs.

[0056] Also provided herein are pharmaceutical compositions suitable for single unit dosages that comprise a compound of the disclosure or its pharmaceutically acceptable stereoisomer, salt, or tautomer and a pharmaceutically acceptable carrier.

[0057] Compositions suitable for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. For instance, liquid formulations of the inventive compounds contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents.

[0058] For tablet compositions, a compound of the present disclosure in admixture with non-toxic pharmaceutically acceptable excipients is used for the manufacture of tablets.

Examples of such excipients include without limitation inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known coating techniques to delay disintegration and absorption in the gastrointestinal tract and thereby to provide a sustained therapeutic action over a desired time period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[0059] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0060] For aqueous suspensions, a compound of the present disclosure is admixed with excipients suitable for maintaining a stable suspension. Examples of such excipients include without limitation are sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia.

[0061] Oral suspensions can also contain dispersing or wetting agents, such as naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0062] Oily suspensions may be formulated by suspending a compound of the present disclosure in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[0063] Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0064] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide a compound of the present disclosure in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0065] Pharmaceutical compositions of the present disclosure may also be in the form of oil-in-water emulsions. The oily phase may 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 may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensaturatedion products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

[0066] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable, an aqueous suspension or an oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0067] The compounds disclosed herein may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0068] Compositions for parenteral administrations are administered in a sterile medium. Depending on the vehicle used and concentration the concentration of the drug in the

formulation, the parenteral formulation can either be a suspension or a solution containing dissolved drug. Adjuvants such as local anesthetics, preservatives and buffering agents can also be added to parenteral compositions.

METHODS OF USE

[0069] The present disclosure provides methods of treating a subject suffering from a disease or condition characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$). The disclosed methods comprise administering to the subject a therapeutically effective amount of any compound as described herein, such as a compound of Formula I or Formulae (Xa), (Xb), (Xc), (Xd), or a compound shown in Table A,Table B, or Table C.

[0070] Transcription of $r(G_4C_2)^{exp}$ leads to accumulation of nuclear foci that sequester various RNA binding proteins (RBPs) such as HNRNPA3, PURA, ADARB2, HNRNPH1 among many others (Jazurek, M., Ciesiolka, A., Starega-Roslan, J., Bilinska, K., and Krzyzosiak, W. J. (2016) Identifying proteins that bind to specific RNAs - focus on simple repeat expansion diseases, *Nucleic Acids Research 44*, 9050-9070; Kumar, V., Hasan, G. M., and Hassan, M. I. (2017) Unraveling the Role of RNA Mediated Toxicity of C9orf72 Repeats in C9-FTD/ALS, *Frontiers in Neuroscience 11*). Consequently, their ability to properly regulate RNA targets is impaired, ultimately leading to global mis-splicing events, defects in RNA metabolism and nucleocytoplasmatic transport. The $r(G_4C_2)^{exp}$ transcripts undergo repeat associated non-ATG (RAN) translation. (Green, K. M., Linsalata, A. E., and Todd, P. K. (2016) RAN translation—What makes it run?, *Brain Research 1647*, 30-42; Cleary, J. D., and Ranum, L. P. W. (2017) New developments in RAN translation: insights from multiple diseases, *Current Opinion in Genetics & Development 44*, 125-134). This non-canonical translation occurs across expanded repeats despite the absence of an ATG initiating codon and results in the production of toxic dipeptide repeats (DPRs) among which poly(GP) was identified as a pharmacodynamic marker in c9ALS patients (Gendron, T. F., *et al.* (2017) Poly(GP) proteins are a useful pharmacodynamic marker for C9ORF72-associated amyotrophic lateral sclerosis, *Science Translational Medicine 9*). Toxic dipeptide repeats are associated with the production of dipeptide repeat proteins. These dipeptide repeat proteins are toxic and prone to aggregation, and are associated with various diseases and disorders, such as Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

[0071] Accordingly, in some aspects, the disclosure provides methods of treating physiological states associated with diseases and disorders such as ALS and FTD. In some cases, the disclosure provides methods of inhibiting RAN translation which produces toxic dipeptide repeat proteins. In some cases, the disclosure provides methods of inhibiting

nuclear foci. In some cases, the disclosure provides methods of rescuing nuclear pore dysfunction. In some cases, the disclosure provides methods of rescuing protein localization.

[0072] Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are fatal neurodegenerative disorders that share common clinical pathologies and genetic causes (Taylor, J. P., Brown Jr, R. H., and Cleveland, D. W. (2016) Decoding ALS: from genes to mechanism, *Nature 539*, 197-206). Both disorders are highly heterogeneous with respect to underlying causal genetics, site and age onset (Swinnen, B., and Robberecht, W. (2014) The phenotypic variability of amyotrophic lateral sclerosis, *Nat Rev Neurol 10*, 661-670), partially explaining the lack of approved drugs despite more than 20 years of ALS research (Petrov, D., Mansfield, C., Moussy, A., and Hermine, O. (2017) ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment?, *Frontiers in Aging Neuroscience 9*). The discovery of G4C2 hexanucleotide repeat expansions ($r(G_4C_2)^{exp}$) in the non-coding region of *C9ORF72* gene is the most common cause of ALS/FTD, designated c9ALS/FTD (DeJesus-Hernandez, M. *et al.* (2011) Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS, *Neuron 72*, 245-256; Renton, Alan E *et al.* (2011) A Hexanucleotide Repeat Expansion in C9ORF72 Is the Cause of Chromosome 9p21-Linked ALS-FTD, *Neuron 72*, 257-268). Healthy individuals carry up to 30 G_4C_2 sequences, whereas c9ALS/FTD disease phenotypes are triggered by hundreds to thousand such repeats (Beck, J. *et al.* (2013) Large C9orf72 Hexanucleotide Repeat Expansions Are Seen in Multiple Neurodegenerative Syndromes and Are More Frequent Than Expected in the UK Population, *The American Journal of Human Genetics 92*, 345-353; van Blitterswijk, M. *et al.* Association between repeat sizes and clinical and pathological characteristics in carriers of C9ORF72 repeat expansions (Xpansize-72): a cross-sectional cohort study, *The Lancet Neurology 12*, 978-988).

[0073] The present disclosure is predicated, in some embodiments, upon the discovery of small molecule compounds described herein that selectively inhibit repeat associated non-ATG (RAN) translation. Accordingly, the compounds are useful in treating diseases that are characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$). Thus, in some embodiments, the disease or condition is amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD).

EXAMPLES

[0074] **TR-FRET hnRNP H Binding Assay**. The TR-FRET assays were performed as previously described (Disney et al., 2012) except the final concentrations of biotinylated

r(G_4C_2)$_8$(SEQ ID NO: 2) RNA and hnRNP H1-His$_6$ were 80 nM and 75 nM, respectively. The RNA was folded by heating to 95 °C for 5 min in 1× Folding Buffer followed by slowly cooling to room temperature. The buffer was adjusted to 1×TR-FRET Assay Buffer followed by addition of compound. The mixture was incubated for 15 min at room temperature and then hnRNP H1-His$_6$ was added. After an additional 15 min incubation, streptavidin-XL665 (HTRF, Cisbio Bioassays) and anti-His$_6$-Tb (HTRF, Cisbio Bioassays) were added to a final concentration of 40 nM and 0.44 ng/μL, respectively. After incubating for 1 h, TR-FRET was measured as previously described. The IC$_{50}$s were either calculated by fitting the equation (1) in Graphpad Prism.

$$y = B + \frac{A-B}{1+\left(\frac{IC50}{x}\right)^{hillslope}} \quad \text{(eq. 1)}$$

[0075] **Cell culture.** The HEK293T cells were cultured in 1× DMEM containing 4.5 g/L glucose, 10% FBS, 2 mM L-glutamine, and 1×apenicillin/streptomycin (growth medium) at 37 °C in 5% CO_2.

[0076] **Cell-based assay to assess RAN translation and Poly(GP) response**. The HEK293T cells (80% confluent) were batch-transfected in growth medium for 4 h with *(G_4C_2)$_{66}$–No ATG–GFP* (SEQ ID NO: 11) and a plasmid encoding mCherry (for normalization) using JetPrime transfection reagent (Polyplus) according to the manufacturer's instructions. The cells were then seeded into a 384-well plate and incubated for 2 h before addition of compound using Biomek NXP Laboratory Automation Workstation that was equipped with a 100 nL 384-pin head. After treatment for 24 h, the medium was removed, and the cells were lysed in 100 mM potassium phosphate lysis buffer, pH 7.8, and 0.2% Triton X-100. Fluorescence was measured using a BioTek FLx800 with 530/25 nm (excitation) and 590/35 nm (emission) filters for mCherry and 485/20 nm (excitation) and 528/20 nm (emission) filters for GFP. Background was determined by measuring the corresponding fluorescence intensities in untransfected cells. The background-corrected ratio of GFP to mCherry was used to determine the effect of compound on RAN translation. Poly (GP) measurement was followed by previous protocol.(Su et al., 2014) The HEK293T cells were batch-transfected with *(G_4C_2)$_{66}$* (SEQ ID NO: 11) *or (TG_4C_2)$_{62}$* plasmid and were treated different concentration of compound. Data from this assay is presented in Table C.

[0077] **Effect of compound treatment on (G_4C_2)$_{66}$ (SEQ ID NO: 11)–No ATG–GFP transcript levels.** Approximately 2×10^6 HEK293T cells were plated in 60 mm cell culture dishes and transfected with 3.5 μg *(G_4C_2)$_{66}$–No ATG–GFP* (SEQ ID NO: 11)plasmid using JetPrime transfect agent per manufacturer's protocol. After 4 h, cells were trypsinized and plated into 48-well plates in growth medium. After an additional 2 h, the compound of

interest or vehicle were added in growth medium. After overnight incubation, the compound-containing medium was removed, and cells were washed with 1× Dulbecco's phosphate-buffered saline (DPBS). Total RNA was harvested with a Quick RNA™ Mini-Prep Kit (Zymo Research) per the manufacturer's recommended protocol.

[0078] The cDNA was generated from 100 ng RNA using a QScript cDNA Synthesis Kit (Quanta Biosciences) according to manufacturer's recommended procedure; qPCR was completed with Power SYBR Green PCR Master Mix (Life Technologies) and 1 µL of 10-fold diluted cDNA on an Applied Biosystems 7900HT Fast Real Time PCR System. The levels of *$(G_4C_2)_{66}$–No ATG–GFP* (SEQ ID NO: 11) were measured with primers specific for GFP and normalized to 18S or β-actin values. Table S3 lists the sequences of all PCR primers.

[0079] **CD spectroscopy**. The CD spectroscopic experiments were conducted using a spectropolarimeter (J-815 Jasco) with a bandwidth of 2 nm at a scan speed of 50 nm/min and a step resolution of 0.2 nm over the spectral range of 210–450 nm. The RNA sample concentration was 10 to 20 µM in 10 mM Na_2HPO_4 buffer with 50 mM LiCl. Thermal melting curves were recorded by a peltier thermal coupler chamber (Jasco), was monitored at 26 5nm between 20 and 95 °C with a temperature ramping rate of 1°C/min rate. The observed signals were baseline subtracted, and the first derivative zero points were defined as the melting temperature. Shape analysis of the melting curves yielded Van't Hoff enthalpy (ΔH_{vH}) using standard procedures (Marky and Breslauer, 1987). The cooperativity of binding of a compound to r(G_4C_2) repeats was measured by plotting the normalized signal intensity at 300 nm or 330 nm in CD spectra as a function of the molar ratio of ([compound]/ [RNA]) and fitted to the following equation:

$$y = x_0 + (x^{n_{Hill}})/(x^{n_{Hill}} + K^{n_{Hill}}) \quad \text{(eq. 2)}$$

where y is the normalized signal intensity, x_o is initial molar ratio of ([compound]/ [RNA]); x is the molar ratio of ([compound]/ [RNA]), n_{Hill} is Hill coefficient, and K is the Hill binding constant.

[0080] In some embodiments, RNA (5 µM final concentration) was annealed at 95 °C for 4 min in 100 mM LiCl and 10 mM sodium phosphate buffer (pH = 7) and let to cool down to room temperature. CD spectra were recorded upon dose dependent addition of compound (from 10 mM stock solution in 100% DMSO) on a JASCO J-815 spectrometer using a 10 mm cuvette and PMT CD detector. Data was collected at 25 °C by acquiring the CD signal within 210-500 nm range at a scanning speed of 50 nm / min using standard sensitivity, band width of 1 nm and D.I.T. of 1 s.

[0081] **Gel shift assay.** Gel shift assays were performed using self-cast 15% native PAGE gel. Briefly, RNAs (80 μM final concentration) were annealed at 95 °C for 4 min in 10 mM sodium phosphate buffer (pH = 7) and let to cool down to room temperature. Samples were loaded on gel and ran at 125 V for 1 hour at room temperature using 1 × TBE buffer. Bromophenol blue and xylene cyanol were used as size markers. Bands were visualized using UV lamp.

[0082] **RNA FISH and immunostaining: nuclear foci.** The RNA FISH and hnRNP H immunostaining were completed as previously described.(Lee et al., 2013) Briefly, HEK293T cells (80% confluent) were batch-transfected as described above. The cells were then seeded into 12-well plates with coverslips and incubated for 2 h before addition of compound. After incubation with compound for 24 h, the cells were fixed in 4% paraformaldehyde for 15 min and washed 5 times with 1× DPBS. After washing with 1× DPBS for 15 min at room temperature, the cells were washed with 0.1% Triton X-100 in 1× DPBS for 5 min at room temperature followed by washing with 40% formamide in 2× SSC buffer for 15 min at room temperature. The RNA FISH probe was then added (5 ng/μL of 5'-cy3-d$(G_2C_4)_8$-3') in 40% formamide in 2× SSC containing 8 μg/mL BSA, 66 μg/mL yeast tRNA, and 2 mM vanadyl complex. The samples were incubated at 48 °C and 5% CO_2 overnight. Following overnight hybridization, the cells were washed three times with 2× SSC and then three times with 1× DPBS at room temperature for 15 min each. To immunostain hnRNP H, cells were fixed with 2% (v/v) formaldehyde in 1× DPBS, permeabilized with 0.1% (v/v) Triton X-100 in 1× DPBS, blocked with 5% goat serum for 40 min, and then incubated with a 1:250 dilution of anti-hnRNP H (Novus Bio) in 1× DPBS for 1 h at room temperature. After washing with 1× DPBS twice, the cells were incubated with a 1:250 dilution anti-rabbit IgG DyLight 650 in 1× DPBS at room temperature for 1 h. After washing (1× DPBS three times at room temperature for 15 min each), cells were stained with 1 μg/mL DAPI in 1× DPBS for 10 min at room temperature and then washed again with 1× DPBS immediately before imaging. Images were collected using an Olympus Fluoview 1000 confocal microscope.

[0083] **Foci Imaging by Compound and BG4, a G-quadruplex antibody**. Briefly, HEK293T cells (80% confluent) were batch-transfected as described above. The cells were then seeded into 12-well plates with coverslips and incubated for 2 h before addition of compound. After incubation with compound for 24 h, the cells were fixed in 2% paraformaldehyde for 15 min and washed five times with 1× DPBS. The cells were then washed with 0.1% Triton X-100 in 1× DPBS for 5 min and three times with 1× DPBS. **Compound** (0.5 μM) was added to the cells for 2 h at 37 °C.

[0084] For experiments employing compound or RNase, the cells were incubated compound (5 μM for 24 h) or RNase, the cells were incubated an RNase solution (25 mg/ ml in 1× DPBS) at 37 °C for 2 h and washed 2 times with 1× DPBS before treatment with compound. For BG4 studies,(Moye et al., 2015) the cells were fixed with 2% (v/v) formaldehyde in 1× DPBS, permeabilized with 0.1% (v/v) Triton X-100 in PBS, and blocked with 2% (w/v) milk in 1× DPBS. After washing with 1× DPBS twice, the slides were incubated with BG4 primary antibody (600 nM) for 1 h at 37 °C, and washed three times for 5 min with 0.01% Tween-20 in 1× DPBS and then overlaid with secondary antibody (Rabbit anti-flag Tag antibody, Cell Signaling; 1:800 dilution) for 1 h at 37 °C. After washing three times with 0.01% Tween-20 in 1× DPBS, the cells were incubated with anti-rabbit IgG DyLight 650. The cells were stained with 1 μg/ mL DAPI in 1× DPBS for 10 min at room temperature and then washed with 1× DPBS. Images were collected using an Olympus Fluoview 1000 confocal microscope.

[0085] **Polysome profiling**. Polysome profiling studies were completed similarly to previously described methods (Yang et al., 2016; Yang et al., 2015). Briefly, 100 mm dishes were plated with 4.5×10^6 HEK293T cells and batch-transfected as described above. Approximately 2 h after plating, cells were treated with vehicle or compound (5 μM) and incubated for 16-18 h. Cells were then lysed with 250 μL of ice-cold Cell Lysis Buffer [10 mM NaCl, 10 mM $MgCl_2$, 10 mM Tris, pH 7.5, 1% Triton X-100, 1% sodium deoxycholate, 1 mM DTT supplemented with 0.1 mg/L cycloheximide and 0.2 U/μL RNAsin (Promega)]. The lysate was transferred to an Eppendorf tube, gently vortexed and centrifuged for 5 min at 13,200 rpm and 4 °C. The supernatant was transferred to a new tube and stored at -80 °C until further use.

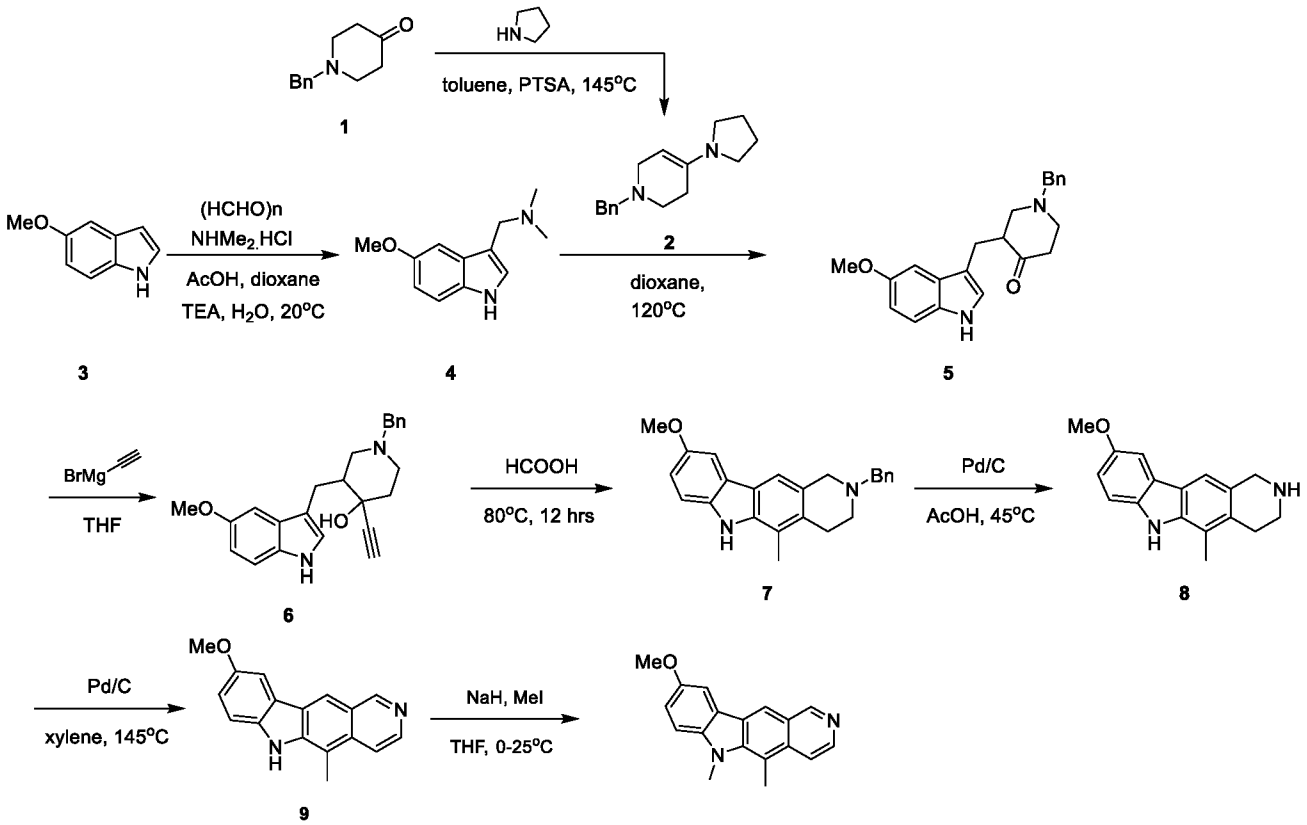
[0086] Cellular lysates were separated using a 10-50% sucrose gradient in 500 μL fractions. A 100 μL aliquot from each fraction was removed and the RNA isolated by using a Quick RNA™ Mini-Prep (Zymo Research) according to manufacturer's protocol. cDNA was generated from 250 ng of RNA using a QScript cDNA Synthesis Kit according to manufacturer's recommended procedure. The levels of *$(G_4C_2)_{66}$–No ATG–GFP* (SEQ ID NO: 11) mRNA in each fraction were measured by qPCR as described above with primers specific for GFP. Data from vehicle- and compound-treated samples were normalized as follows: triplicate C_t values were averaged and ΔC_t values were calculated by comparison to β-actin; $\Delta\Delta C_t$ values were afforded by comparing treated to untreated ΔC_t values. Data were then normalized to the fraction with the lowest abundance of GFP.

[0087] **In vitro translation assay**. The RNA template for translational assays was transcribed from the *$(G_4C_2)_{66}$–No ATG–NanoLuc* (SEQ ID NO: 11) plasmid using an in vitro transcription system (RiboMax, Promega). In vitro translation reactions (50 μL) using the

Flexi Rabbit Reticulocyte Lysate System (Promega) were programmed with 4µg *$(G_4C_2)_{66}$–No ATG–NanoLuc* (SEQ ID NO: 11) RNA and 1µg Firefly Luciferase RNA (Promega) as the template. The RNA was folded into the G-quadruplex form in buffer containing KCl (384 mM) by heating at 95 °C for 10 min followed by slow cooling to 25 °C in a total volume of 10 µL. The RNA was folded into the hairpin form in buffer by placing on ice. (NMR spectroscopy shows that only the hairpin is formed at low temperatures.) After folding, the RNA was added to the reticulocyte lysate, amino acid mixtures, and RNasin ribonuclease inhibitor (Promega) in a total volume of 50 µL (manufacturer's protocol). Translation proceed for 90 min at 30 °C for 90 min and then luciferase activity was measured. The reactions were diluted in Glo Lysis Buffer followed by addition of Nano-Glo substrate (Promega).

EXAMPLE 1

[0088] 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole:



Step 1: benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine

[0089] To a solution of 1-benzylpiperidin-4-one (350 g, 1.8 mol, 343.1 mL, 1 eq), pyrrolidine (197.1 g, 2.7 mol, 231.4 mL, 1.5 eq) in toluene (1000 mL) was added PTSA (968.3 mg, 5.6 mmol, 3 eq). The mixture was stirred at 140°C for 12 hr. TLC indicated one major new spot with lower polarity was detected. The reaction mixture was concentrated under reduced

pressure to remove solvent and to give 480 g of crude benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine.

Step 2: 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[0090] A mixture of 5-methoxy-1H-indole (50 g, 339.7 mmol, 1 eq, 2 batch), formaldehyde (30.3 g, 373.7 mmol, 27.8 mL, 37% purity, 1.1 eq), N-methylmethanamine;hydrochloride (30.4 g, 373.7 mmol, 1.1 eq), TEA (37.8 g, 373.7 mmol, 52.0 mL, 1.1 eq), AcOH (30.6 g, 509.6 mmol, 29.1 mL, 1.5 eq) in dioxane (300 mL) and H_2O (300 mL) was stirred at 20°C for 12 hr. LC-MS showed 89.8% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove dioxane. The aqueous was added to NaOH.aq (100 mL, 2M) at 25°C and then the mixture was filtered and the filter cake was concentrated under reduced pressure to give 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine.

Step 3: 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[0091] A solution of 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine (50 g, 244.7 mmol, 1 eq, 2 batch) in dioxane (400 mL) was added 1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine (148.3 g, 611.9 mmol, 2.5 eq), then the mixture was stirred at 120°C for 12 hr. LC-MS showed 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (200 mL) and extracted with EtOAc (100 mL × 5). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~60 % Ethyl acetate / Petroleum ether) to give 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl) piperidin-4-one.

Step 4: 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[0092] A mixture of 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one (40 g, 114.8 mmol, 1 eq) in THF (500 mL) was added bromo(ethynyl)magnesium (0.5 M, 918.3 mL, 4 eq) at 0°C and then the mixture was stirred at 0°C for 2 hr under N_2 atmosphere. LC-MS showed 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by addition aq. NH_4Cl (150 mL) at 20 °C, and extracted with EtOAc (100 ml × 5). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (42 g, 112.1 mmol).

Step 5: 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[0093] A solution of 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (42 g, 112.1 mmol, 1 eq) in HCOOH (500 mL) was stirred at 80°C for 12 hr. TLC indicated 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol was consumed completely and many new spots formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (50 mL), adjusted pH to 8 with sat $NaHCO_3$ and extracted with EtOAc (100 mL × 5). The combined organic layers were washed with brine (30 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~100 % Ethyl acetate / Petroleum ether gradient @ 120 mL/min) to afford 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 6: 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[0094] A solution of 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (5.3 g, 14.8 mmol, 1 eq) in AcOH (60 mL) was added Pd/C (3 g, 14.87 mmol, 10% purity). The mixture was stirred at 45°C for 2 hr under H_2 (15 psi). LCMS showed the reaction was completed and main peak with desired product. The mixture was filtered and concentrated under reduced pressure to give 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido [4,3-b]carbazole (as AcOH salt).

Step 7: 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

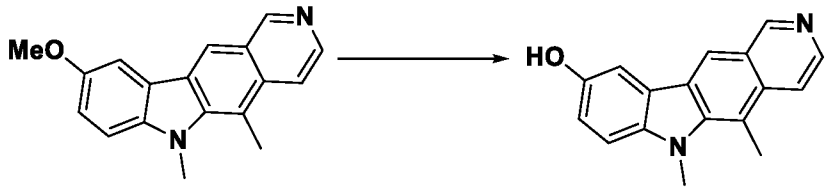
[0095] To a solution of 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido [4,3-b]carbazole (3.5 g, 10.7 mmol, 1 eq, HOAC) in xylene (100 mL) was added Pd/C (2 g, 10.72 mmol, 10% purity, 1 eq). The mixture was stirred at 145°C for 12 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was filtered and concentrated under reduced pressure to give 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole.

Step 8: 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[0096] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (2.2 g, 8.3 mmol, 1 eq) in THF (40 mL) was added NaH (1.0 g, 25.1 mmol, 60% purity, 3 eq) and MeI (1.1 g, 8.3 mmol, 522.1 uL, 1 eq) at 0 °C. Then the mixture was stirred at 25°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into NH_4Cl (100 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b] carbazole.

EXAMPLE 2

[0097] **5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol**



[0098] To a solution of E-1780 (500 mg, 1.81 mmol) in DCM (20 ml) was added BBr3 (1.7 ml, 18 mmol) at 0 °C and warmed to rt and stirred overnight. The mixture was added NH4OH aq (10%) and added DCM. The combined org phase was washed with brine, dried over Na2SO4 and concentrated in vacuo. The part of residue was purified with HPLC and the rest was used in further reaction as crude.

Preparatory reverse-phase HPLC Method

[0099] Reverse-phase high pressure liquid chromatography (HPLC) purification was performed using a Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.

EXAMPLE 3

9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b] carbazole:

To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (400 mg, 1.5 mmol, 1 eq) in DMF (10 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole;hydrochloride (283.6 mg, 1.8 mmol, 1.2 eq), $LiOH.H_2O$ (255.9 mg, 6.1 mmol, 4 eq) and NaI (228.5 mg, 1.5 mmol, 1 eq). The mixture was stirred at 80 °C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,10min) to afford 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b] carbazole.

MS (ESI): m/z = 345.0 $[M+H]^+$

EXAMPLE 4

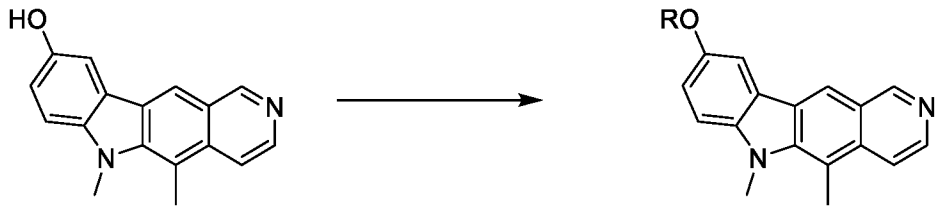
N-(2-aminoethyl)-2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetamide (4a) and 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetic acid (4b)

[00100] To a solution of 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b] (17 mg, 0.05 mmol) in DMF was added LiOH-H2O (4 mg, 0.1 mmol) and the mixture was heated at 70 °C for 6 h and then purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford 4a and 4b.

4a: MS (ESI): 363.2 $[M+H]^+$

4b: MS (ESI): 321.1 $[M+H]^+$

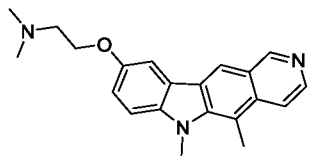
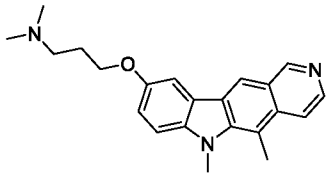
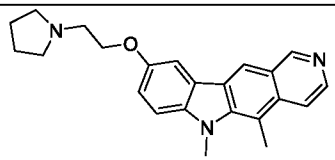
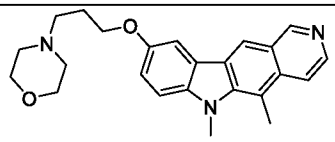
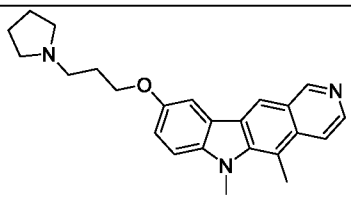
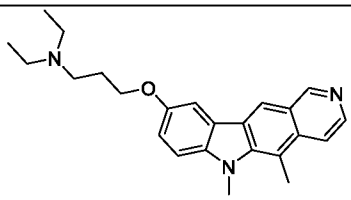
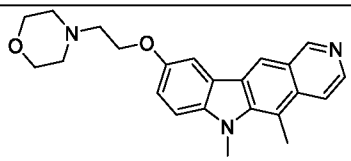
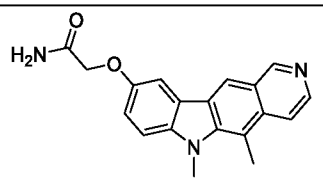
EXAMPLES 5-13

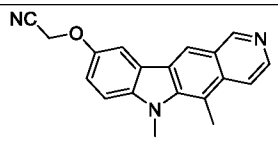


General procedure for preparation of compounds 5-13

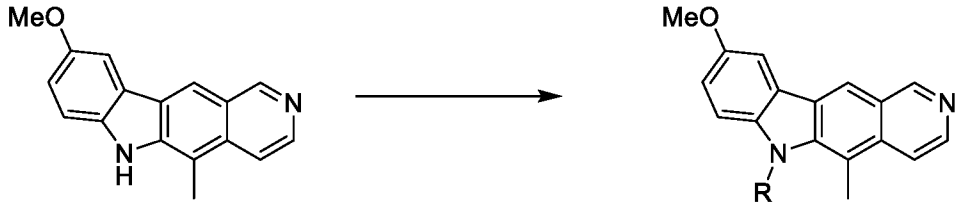
[00101] To a solution of the product of Example 2 (52 mg, 0.20 mmol) in DMF (1 ml) was added LiOH·H2O (21 mg, 0.50 mmol) and NaI (2 mg, 0.013 mmol) and alkyl chloride (R-Cl, 0.25 mmol) and the mixture was heated at 70 °C for 4 h. The mixture was purified by HPLC (Reverse-phase high pressure liquid chromatography (HPLC) purification was performed using a Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the product shown in table below:

Example #	Compound Name	MS (ESI)	Structure

5	(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylethan-1-amine	334.5 [M+H]+	
6	3-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylpropan-1-amine	348.5 [M+H]+	
7	5,6-dimethyl-9-(2-(pyrrolidin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole	457.6 [M+H]+	
8	4-(3-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propyl)morpholine	390.5 [M+H]+	
9	5,6-dimethyl-9-(3-(pyrrolidin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole	374.5 [M+H]+	
10	3-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-diethylpropan-1-amine	376.5 [M+H]+	
11	4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine	376.5 [M+H]+	
12	2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetamide	320.1 [M+H]+	

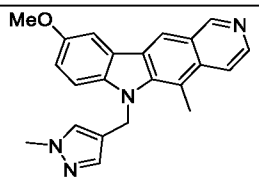
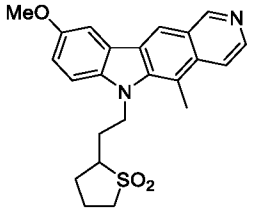
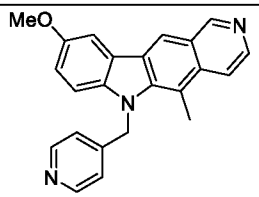
13	2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetonitrile	302.4 [M+H]+	

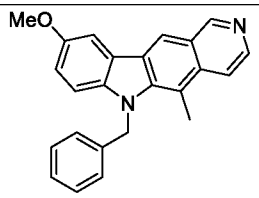
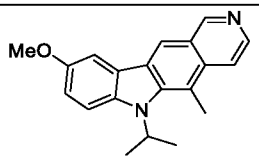
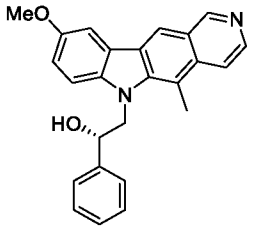
EXAMPLES 14 - 19



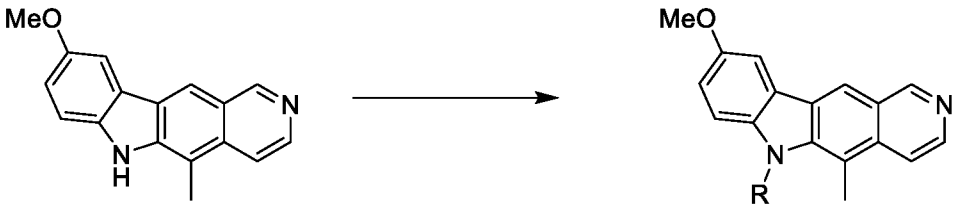
General procedure for preparation of compounds 14 - 19

[00102] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (26 mg, 0.1 mmol; Example 1, step 7) in THF (1 ml) was added KOtBu (22 mg, 0.2 mmol), NaI (15 mg, 0.1 mmol) and electrophile (0.2 mmol) and the mixture was stirred at rt overnight, then purified by prep HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the product as shown in the Table below.

Example #	Compound Name	Structure
14	9-methoxy-5-methyl-6-((1-methyl-1H-pyrazol-4-yl)methyl)-6H-pyrido[4,3-b]carbazol	
15	3-(2-(9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethyl)tetrahydrothiophene 1,1-dioxide	
16	9-methoxy-5-methyl-6-(pyridin-4-ylmethyl)-6H-pyrido[4,3-b]carbazole	

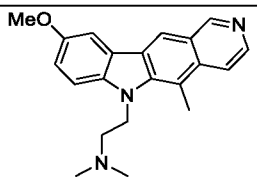
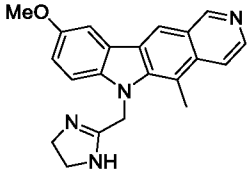
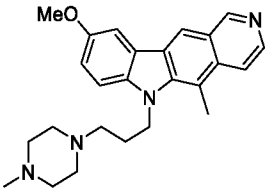
17	6-benzyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole	
18	6-isopropyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole	
19	(S)-2-(9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)-1-phenylethan-1-ol	

EXAMPLES 20 – 22



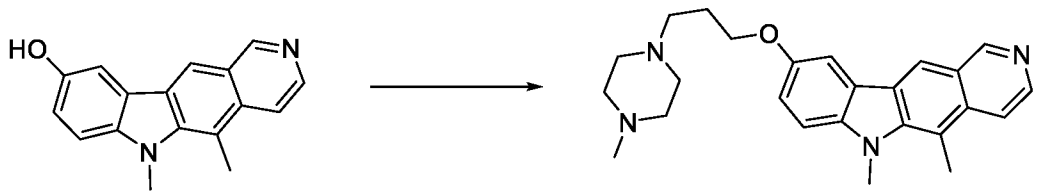
General procedure for preparation of compounds 20 - 22

[00103] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (26 mg, 0.1 mmol; Example 1, step 7) in THF was added NaH (8 mg, 0.20 mmol) and NaI (1.5 mg, 0.01 mmol), alkyl chloride (0.2 mmol) and the mixture was stirred at rt overnight and then purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the product as shown in the table below.

Example #	Compound Name	Structure
20	2-(9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)-N,N-dimethylethan-1-amine	
21	6-((4,5-dihydro-1H-imidazol-2-yl)methyl)-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole	
22	9-methoxy-5-methyl-6-(3-(4-methylpiperazin-1-yl)propyl)-6H-pyrido[4,3-b]carbazole	

EXAMPLE 23

[00104] 5,6-dimethyl-9-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole

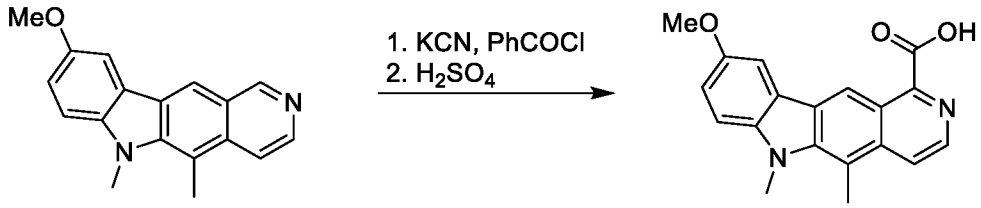


5,6-dimethyl-9-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole

[00105] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (26 mg, 0.10 mmol) in DMF (1 ml) was added LiOH·H2O (21 mg, 0.50 mmol) and NaI (2 mg, 0.013 mmol) and 1-(3-chloropropyl)-4-methylpiperazine (44 mg, 0.25 mmol) and the mixture was heated at 70 °C for 4 h. The mixture was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the product.

EXAMPLE 24

9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid



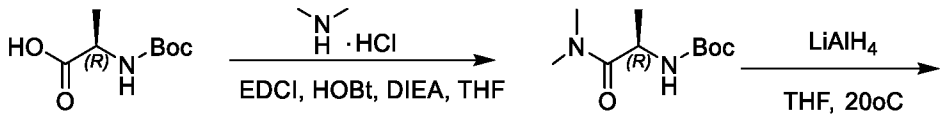
9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

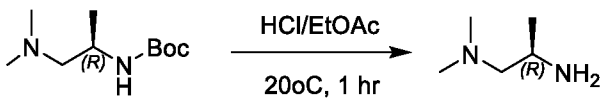
[00106] To a solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (11 mg, FW: 320.21, 0.039 mmol) and KCN (7 mg, 0.1 mmol) in water (0.5 ml) and DCM (0.5 ml) was added benzoyl chloride (6 uL, 0.05 mmol) at 0 °C, then the mixture was warmed to RT, stirred for 2 h, and then added water and DCM. The org phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was added H_2SO_4/H_2O (1:1. 1 ml) and heated at 110 °C overnight. The mixture was purified with RP-HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H_2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the desired product.

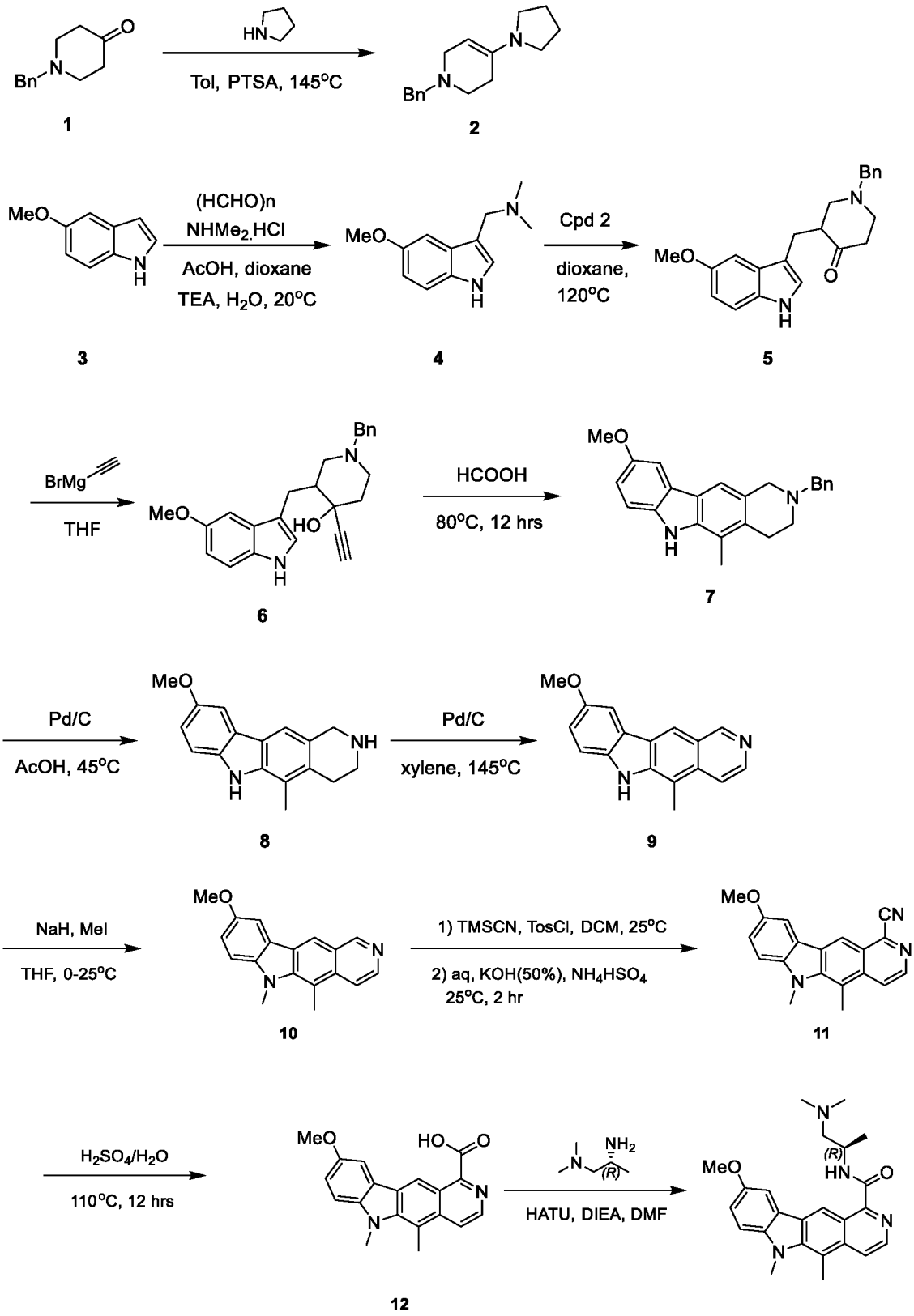
MS (ESI): 321.4

EXAMPLE 25

[00107] (R)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide







Step 1: (R)-tert-butyl (1-(dimethylamino)-1-oxopropan-2-yl)carbamate

[00108] To a solution of (2R)-2-(tert-butoxycarbonylamino)propanoic acid (20 g, 105.7 mmol, 1 eq) in THF (400 mL) was added DIEA (54.6 g, 422.8 mmol, 73.6 mL, 4 eq), EDCI (30.4 g, 158.5 mmol, 1.5 eq), HOBt (21.4 g, 158.5 mmol, 1.5 eq) and N-methylmethanamine

(8.6 g, 105.7 mmol, 9.6 mL, 1 eq, HCl). The mixture was stirred at 20°C for 12 hr. TLC indicated one major new spot was detected. The reaction mixture was partitioned between H_2O (500 mL) and EtOAc (500 mL). The aqueous phase was washed with EtOAc (300 mL × 3). The organic phase was separated and washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @50mL/min) to give (R)-tert-butyl (1-(dimethylamino)-1-oxopropan-2-yl)carbamate **2b**.

Step 2: (R)-tert-butyl (1-(dimethylamino)propan-2-yl)carbamate

[00109] To a solution of tert-butyl N-[(1R)-2-(dimethylamino)-1-methyl-2-oxo-ethyl]carbamate (20.3 g, 93.8 mmol, 1 eq) in THF (400 mL) was added $LiAlH_4$ (7.1 g, 187.7 mmol, 2 eq) at 0°C. The mixture was stirred at 20°C for 2 hr. TLC indicated one major new spot was detected. The reaction was quenched with saturated $MgSO_4$ (7.1 mL) and $MgSO_4$ (20 g) solid was added. The mixture was filtered and the cake was washed with ethyl acetate (200 mL × 3). The combined filtrate was concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate / Petroleum ether gradient @ 100mL/min) to give (R)-tert-butyl (1-(dimethylamino)propan-2-yl)carbamate **3a**.

Step 3: (R)-N1,N1-dimethylpropane-1,2-diamine

[00110] A solution of tert-butyl N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]carbamate (3.5 g, 17.3 mmol, 1 eq) in HCl/EtOAc (30 mL, 4 mol/L) was stirred at 20°C for 1 hr. TLC indicated one major new spot was detected. The reaction mixture was concentrated under reduced pressure to give (R)-N1,N1-dimethylpropane-1,2-diamine **4a**.

Step 4: benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine

[00111] To a solution of 1-benzylpiperidin-4-one (350 g, 1.8 mol, 343.1 mL, 1 eq), pyrrolidine (197.1 g, 2.7 mol, 231.4 mL, 1.5 eq) in toluene (1000 mL) was added PTSA (968.3 mg, 5.6 mmol, 3 eq). The mixture was stirred at 140°C for 12 hr. TLC indicated one major new spot with lower polarity was detected. The reaction mixture was concentrated under reduced pressure to remove solvent and to give 480 g of crude benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine **2**.

Step 5: 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[00112] A mixture of 5-methoxy-1H-indole (50 g, 339.7 mmol, 1 eq, 2 batch), formaldehyde (30.3 g, 373.7 mmol, 27.8 mL, 37% purity, 1.1 eq), N-methylmethanamine;hydrochloride (30.4 g, 373.7 mmol, 1.1 eq), TEA (37.8 g, 373.7 mmol,

52.0 mL, 1.1 eq), AcOH (30.6 g, 509.6 mmol, 29.1 mL, 1.5 eq) in dioxane (300 mL) and H_2O (300 mL) was stirred at 20°C for 12 hr. LC-MS showed 89.8% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove dioxane. The aqueous was added to NaOH.aq (100 mL, 2M) at 25°C and then the mixture was filtered and the filter cake was concentrated under reduced pressure to give 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine **4.**

Step 6: 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[00113] A solution of 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine (50 g, 244.7 mmol, 1 eq, 2 batch) in dioxane (400 mL) was added 1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine (148.3 g, 611.9 mmol, 2.5 eq), then the mixture was stirred at 120°C for 12 hr. LC-MS showed 1-(5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine was consumed completely and one main peak with desired m/z was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (200 mL) and extracted with EtOAc (100 mL × 5). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Eluent of 0~60 % Ethyl acetate / Petroleum ether) to give 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl) piperidin-4-one **5**

Step 7: 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[00114] A mixture of 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one (40 g, 114.8 mmol, 1 eq) in THF (500 mL) was added bromo(ethynyl)magnesium (0.5 M, 918.3 mL, 4 eq) at 0°C and then the mixture was stirred at 0°C for 2 hr under N_2 atmosphere. LC-MS showed 1-benzyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one was consumed completely and one main peak with desired m/z was detected. The reaction mixture was quenched by addition aq. NH_4Cl (150 mL) at 20 °C, and extracted with EtOAc (100 ml × 5). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol **6**.

Step 8: 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00115] A solution of 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (42 g, 112.1 mmol, 1 eq) in HCOOH (500 mL) was stirred at 80°C for 12 hr. TLC indicated 1-benzyl-4-ethynyl-3-((5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol was consumed completely and many new spots formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O (50 mL), adjusted pH to 8 with sat $NaHCO_3$ and extracted with EtOAc (100 mL × 5). The combined

organic layers were washed with brine (30 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~100 % Ethyl acetate / Petroleum ether gradient @ 120 mL/min) to afford 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole **7**.

Step 9: 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00116] A solution of 2-benzyl-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (5.3 g, 14.8 mmol, 1 eq) in AcOH (60 mL) was added Pd/C (3 g, 14.87 mmol, 10% purity). The mixture was stirred at 45°C for 2 hr under H_2 (15 psi). LCMS showed the reaction was completed and main peak with desired product. The mixture was filtered and concentrated under reduced pressure to give 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido [4,3-b]carbazole (**8**, as AcOH salt).

Step 10: 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00117] To a solution of 9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido [4,3-b]carbazole (3.5 g, 10.7 mmol, 1 eq, HOAC) in xylene (100 mL) was added Pd/C (2 g, 10.72 mmol, 10% purity, 1 eq). The mixture was stirred at 145°C for 12 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was filtered and concentrated under reduced pressure to give 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole **9**

Step 11: 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00118] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (2.2 g, 8.3 mmol, 1 eq) in THF (40 mL) was added NaH (1.0 g, 25.1 mmol, 60% purity, 3 eq) and MeI (1.1 g, 8.3 mmol, 522.1 uL, 1 eq) at 0 °C. Then the mixture was stirred at 25°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into NH_4Cl (100 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b] carbazole **10**.

Step 12: 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00119] To a solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b] carbazole (2 g, 7.24 mmol, 1 eq) in DCM (40 mL) was added TMSCN (1.8 g, 18.8 mmol, 2.3 mL, 2.6 eq). To this mixture a solution of TosCl (2.6 g, 13.7 mmol, 1.9 eq) in DCM (20 mL) was added at 25 °C. Then the mixture was stirred at 30°C for 12 hr. LCMS showed the intermediate was detected. Then KOH (10 mL, 50% W/W) and NH_4HSO_4 (15 mg) were added. The mixture

was stirred at 25°C for 2 hr. The mixture was extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile **11**.

Step 13: 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

[00120] A solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (2.1 g, 6.9 mmol, 1 eq) in H_2SO_4 (10 mL, 98% purity) and H_2O (10 mL) was stirred at 110 °C for 12 hr.

[00121] LCMS showed the reaction was completed and mainly peak with desired product. The mixture was poured into $NaHCO_3$ (500 ml) and the red solid was separate out. Then the mixture was filtered and collected the solid to afford 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid **12**.

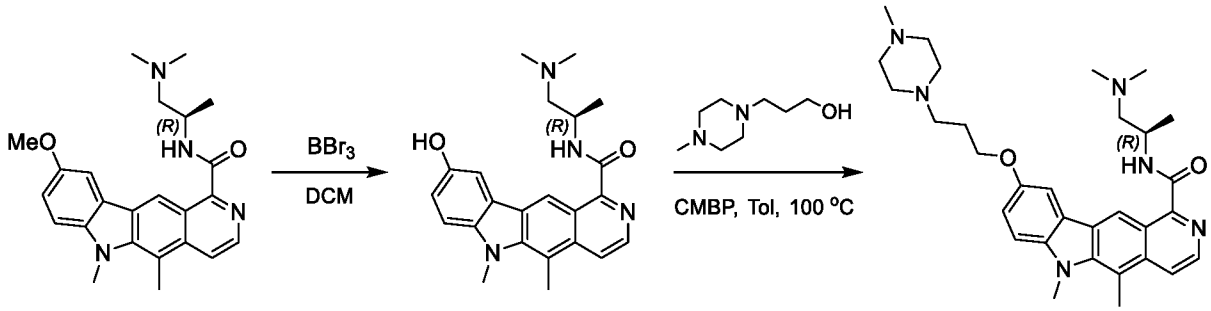
Step 14: (R)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00122] To a solution of 9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxylic acid (1.5 g, 4.6 mmol, 1 *eq*) in DMF (30 mL) was added (2R)-N1,N1-dimethylpropane-1,2-diamine (2.4 g, 14.0 mmol, 3 *eq*, 2HCl), DIEA (3.0 g, 23.4 mmol, 4.0 mL, 5 *eq*). Then HATU (3.5 g, 9.3 mmol, 2 *eq*) was added to the mixture at 0°C. Then the mixture was warmed to 25°C for 1 hrs. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 (250×70mm, 15 um); mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%, 20min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide) or as TFA salt crude product.

MS (ESI): m/z = 405.2 $[M+H]^+$

EXAMPLE 26

(R)-N-(1-(dimethylamino)propan -2-yl)-5,6-dimethyl-9-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide



Step 1: (R)-N-(1-(dimethylamino)propan-2-yl)-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

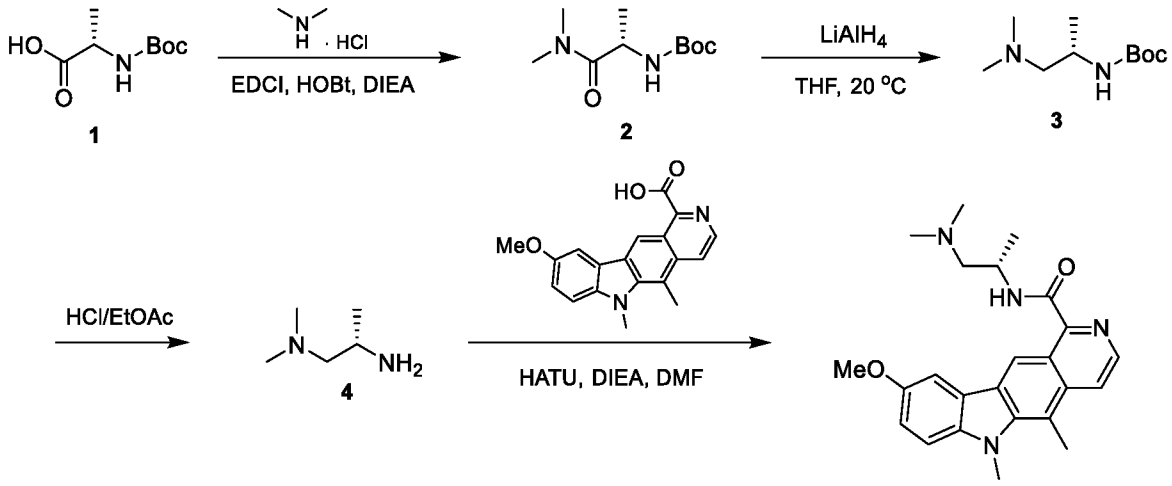
[00123] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido [4,3-b]carbazole-1-carboxamide (0.7 g, 1.3 mmol, 1 eq, TFA) in DCM (100 mL) was added BBr_3 (1.6 g, 6.7 mmol, 650.3 uL, 5 eq) at 0°C. The mixture was stirred at 45°C for 1 hr. LCMS showed the reaction was completed and main peak with desired product. The mixture was poured into NH_4OH (30 mL) and extracted with DCM (100 mL × 3) at 0°C. The combined organic layers were washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (R)-N-(1-(dimethylamino)propan-2-yl)-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

Step 2: (R)-N-(1-(dimethylamino)propan -2-yl)-5,6-dimethyl-9-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00124] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-hydroxy-5,6-dimethyl-pyrido [4,3-b]carbazole-1-carboxamide (340 mg, 870.7 umol, 1 eq) in toluene (10 mL) was added 3-(4-methylpiperazin-1-yl)propan-1-ol (151.5 mg, 957.8 umol, 1.1 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (420.3 mg, 1.7 mmol, 2 eq). The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 10%-30%,8min) to give (R)-N-(1-(dimethylamino)propan -2-yl)-5,6-dimethyl-9-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide (538 mg, contained other batch amount 200 mg, the product solid was dissolved with DMSO and further lyophilization).

MS (ESI): m/z = 531.3 $[M+H]^+$

EXAMPLE 27



Step 1: (S)-tert-butyl (1-(dimethylamino)-1-oxopropan-2-yl)carbamate

[00125] A mixture of (2S)-2-(tert-butoxycarbonylamino)propanoic acid (5 g, 26.4 mmol, 1 eq), N-methylmethanamine (2.1 g, 26.4 mmol, 2.4 mL, 1 eq, HCl), HOBt (5.3 g, 39.6 mmol, 1.5 eq), EDCI (7.6 g, 39.6 mmol, 1.5 eq) and DIEA (13.6 g, 105.7 mmol, 18.4 mL, 4 eq) in THF (50 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25°C for 16 hr under N_2 atmosphere. TLC showed the reaction was completely. The reaction mixture was diluted with water (70 mL) and extracted with ethyl acetate (2 × 70 mL). The combined organic layers were washed with brine (70 mL), dried over anhydrous sodium sulfte, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethylacetate / Petroleum ether gradient @ 100 mL/min) to afford (S)-tert-butyl (1-(dimethylamino)-1-oxopropan-2-yl)carbamate **2**.

Step 2: (S)-tert-butyl (1-(dimethylamino)propan-2-yl)carbamate

[00126] To a solution of (S)-tert-butyl (1-(dimethylamino)-1-oxopropan-2-yl)carbamate (6.5 g, 30.3 mmol, 1 eq) in THF (200 mL) was added $LiAlH_4$ (2.3 g, 60.7 mmol, 2 eq) at 0°C under N_2 atmosphere. The mixture was stirred at 20°C for 2 hr. TLC showed the reaction was completely. The reaction was quenched with saturated $MgSO_4$ (2.3 mL) and 10 g MgSO4 solid was added. The mixture was filtrated and the cake was washed with ethyl acetate (50 mL × 3). The combined filtrate was concentrated to give the crude product. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate / Petroleum ether gradient @ 50 mL/min) to give (S)-tert-butyl (1-(dimethylamino)propan-2-yl)carbamate **3**.

Step 3: (S)-N1,N1-dimethylpropane-1,2-diamine

[00127] A solution of (S)-tert-butyl (1-(dimethylamino)propan-2-yl)carbamate (1.9 g, 9.3 mmol, 1 eq) in HCl/EtOAc (10 mL) (4M) was stirred at 15°C for 2 hr. LCMS showed the reaction was completely. The reaction was concentrated to give the crude product (S)-N1,N1-dimethylpropane-1,2-diamine **4**.

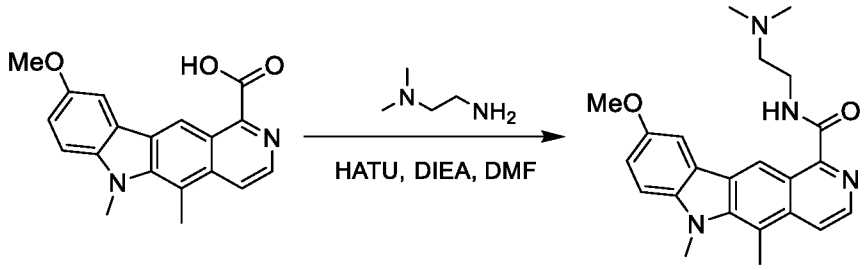
Step 4: (S)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00128] To a solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (80 mg, 249.7 umol, 1 eq) in DMF (3 mL) was added DIEA (161.3 mg, 1.2 mmol, 217.5 uL, 5 eq) and (S)-N1,N1-dimethylpropane-1,2-diamine (131.1 mg, 749.2 umol, 3 eq, 2HCl). The mixture was cooled to 0°C and HATU (284.8 mg, 749.2 umol, 3 eq) was added. The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (FA condition, column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water(0.2%FA)-ACN]; B%: 15%-45%, 9 min) to afford (S)-N-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

MS (ESI): m/z = 405.1 $[M+H]^+$

EXAMPLE 28

N-[2-(dimethylamino)ethyl]-9-methoxy- 5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide



[00129] To a solution of 9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 156.0 umol, 1 eq) in DMF (2 mL) was added N,N-dimethylethane-1,2-diamine (43.1 mg, 488.9 umol, 53.4 uL, 3.1 eq), DIEA (100.8 mg, 780.4 umol, 135.9 uL, 5 eq). Then HATU (118.7 mg, 312.1 umol, 2 eq) was added to the mixture at 0°C and warmed to 25°C for 1 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 35%-55%,6min) to give N-[2-(dimethylamino)ethyl]-9-methoxy- 5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

MS (ESI): m/z = 391.1 $[M+H]^+$

EXAMPLE 29

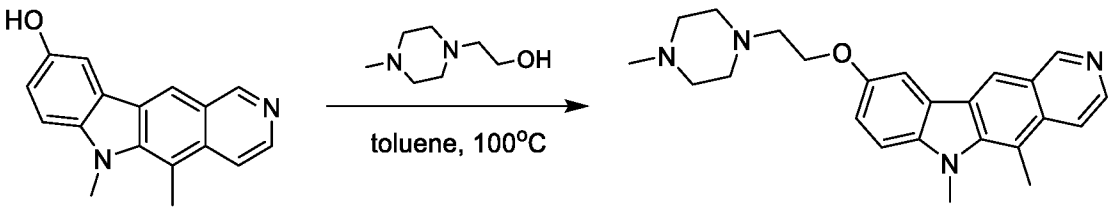
N-(3-(dimethylamino)propyl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00130] To a solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 156.0 umol, 1 *eq*) in DMF (2 mL) was added DIEA (100.8 mg, 780.4 umol, 135.9 uL, 5 *eq*) and N',N'-dimethylpropane-1,3-diamine (47.8 mg, 468.2 umol, 58.5 uL, 3 *eq*). The mixture was cooled to 0°C and HATU (118.7 mg, 312.1 umol, 2 *eq*) was added. The mixture was stirred at 25°Cfor 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (FA condition column: Phenomenex Luna C18 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 25%-55%, 8 min). The residue was purified by prep-HPLC (TFA condition column: Phenomenex Luna C18 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 25%-55%, 8 min) to give N-(3-(dimethylamino)propyl)-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

MS (ESI): m/z = 405.1 $[M+H]^+$

EXAMPLE 30

[00131] 5,6-dimethyl-9-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole

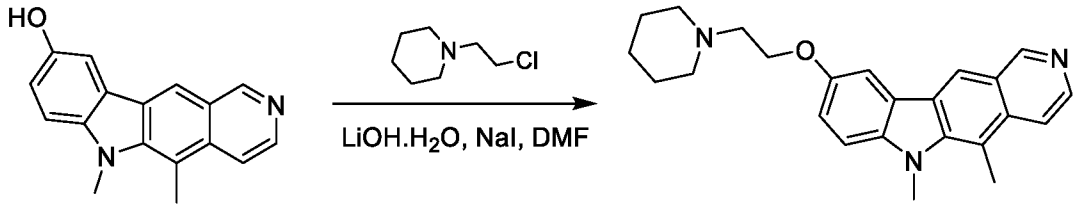


[00132] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (40 mg, 152.4 umol, 1 *eq*) in Tol. (2 mL) was added 2-(4-methylpiperazin-1-yl)ethanol (24.1 mg, 167.7 umol, 1.1 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (110.4 mg, 457.4 umol, 3 *eq*). The mixture was stirred at 100°C for 2 hr under N_2 atmosphere. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition, column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water(0.2%FA)-ACN]; B%: 5%-40%, 9min) to give 5,6-dimethyl-9-(2-(4-methylpiperazin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 389.1 $[M+H]^+$

EXAMPLE 31

5,6-dimethyl-9-(2-(piperidin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole

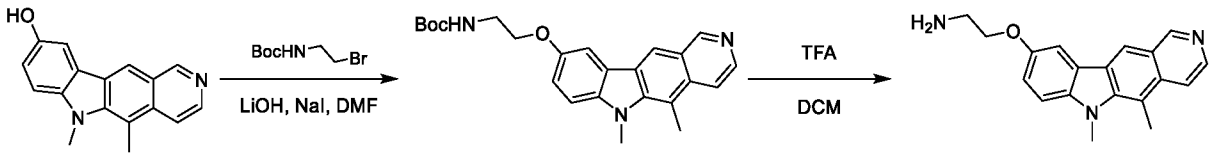


[00133] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 *eq*) in DMF (2 mL) was added $LiOH.H_2O$ (8.0 mg, 190.6 umol, 1 *eq*), NaI (2.8 mg, 19.0 umol, 0.1 *eq*) and 1-(2-chloroethyl)piperidine;hydrochloride (35.0 mg, 190.6 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LCMS showed 5,6-dimethyl-6H-pyrido[4,3-b] carbazol-9-ol has remained, 1-(2-chloroethyl)piperidine;hydrochloride (17.5 mg, 95.3 umol, 0.5 *eq*) and $LiOH.H_2O$ (16.0 mg, 381.2 umol, 2 *eq*) were added to the mixture and stirred for 30min. LC-MS showed **the** desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (**FA condition**, column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water(0.2%FA)-ACN]; B%: 1%-25%,8min) to give 5,6-dimethyl-9-(2-(piperidin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 374.1 $[M+H]^+$

EXAMPLE 32

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine



Step 1: tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)carbamate

[00134] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 eq) in DMF (4 mL) was added $LiOH.H_2O$ (16.0 mg, 381.2 umol, 1 eq), NaI (5.7 mg, 38.1 umol, 0.1 eq) and tert-butyl N-(2-bromoethyl)carbamate (85.4 mg, 381.2 umol, 1 eq). The mixture was stirred at 75°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give crude tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)carbamate.

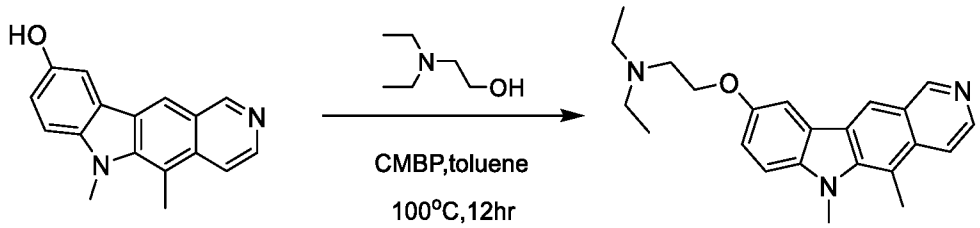
Step 2: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine

[00135] To a solution of tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)carbamate (150 mg, 369.9 umol, 1 eq) in DCM (4 mL) was added TFA (2 mL). The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um; mobile phase: [water (0.1%TFA)-ACN];B%: 1%-30%,8min). The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN];B%: 20%) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine.

MS (ESI): m/z = 306.0 $[M+H]^+$

EXAMPLE 33

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-diethylethanamine

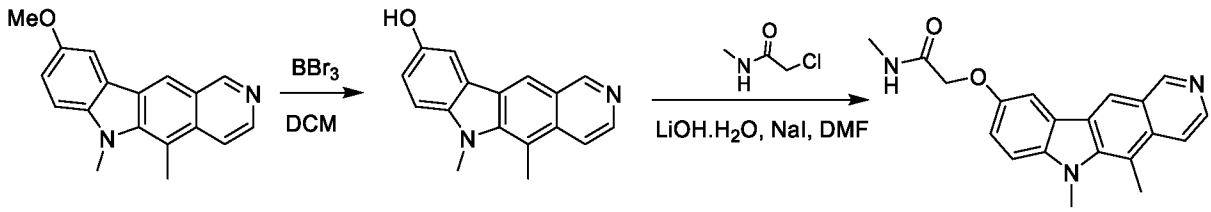


[00136] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 eq), 2-(diethylamino)ethanol (26.8 mg, 228.7 umol, 30.3 uL, 1.2 eq) in toluene (3 mL) was added 2-(tributyl-λ5-phosphanylidene) acetonitrile (69 mg, 285.9 umol, 1.5 eq) under N_2. The mixture was stirred at 100°C for 12 hrs under N_2. LC-MS showed was consumed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 5%-40%,9min) to give 2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N,N-diethyl -ethanamine.

MS (ESI): m/z = 362.1 $[M+H]^+$

EXAMPLE 34

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylacetamide



Step 1: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol

[00137] To a solution of 9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (50 mg, 180.9 umol, 1 eq) in DCM (2 mL) was added BBr_3 (226.6 mg, 904.7 umol, 87.1 uL, 5 eq) at 0°C. The mixture was stirred at 45°C for 12 hrs. LCMS showed the reaction was completely. H_2O (2 mL) and $NH_3.H_2O$ (2 mL) was added to the mixture. The mixture was extracted with DCM (2 mL × 3). The combined organic phase was concentrated to give crude 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol.

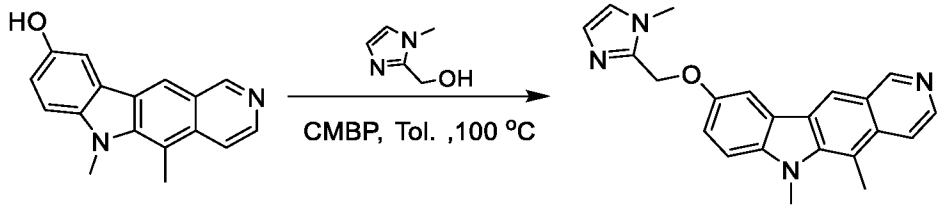
Step 2: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylacetamide

[00138] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (44 mg, 167.7 umol, 1 eq) in DMF (2 mL) was added $LiOH.H_2O$ (7.0 mg, 167.7 umol), NaI (2.5 mg, 16.7 umol, 0.1 eq) and 2-chloro-N-methyl-acetamide (18.0 mg, 167.7 umol, 1 eq). The mixture was stirred at 75°C for 1 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (FA condition, column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water(0.2%FA)-ACN]; B%: 20%-50%, 9min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylacetamide.

MS (ESI): m/z = 334.0 $[M+H]^+$

EXAMPLE 35

5,6-dimethyl-9-((1-methyl-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

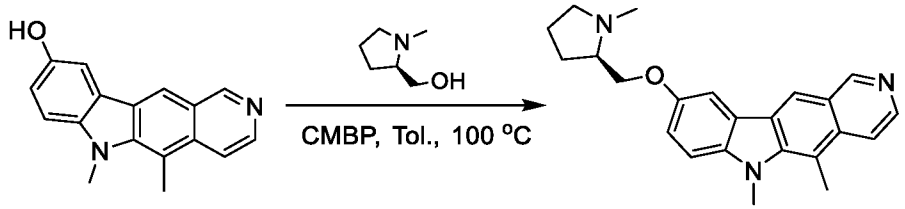


[00139] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 eq) in Tol. (2 mL) was added (1-methylimidazol-2-yl)methanol (42.7 mg, 381.2 umol, 1 eq) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (184.0 mg, 762.4 umol, 2 eq). The mixture was stirred at 100°C for 12 hr. LCMS showed 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol was remained, so 2-(tributyl-λ^5-phosphanylidene)acetonitrile (138.0 mg, 571.8 umol, 1.5 eq) was added to the mixture and stirred at 100°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%, 9 min) to give 5,6-dimethyl-9-((1-methyl-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 357.1 $[M+H]^+$

EXAMPLE 36

(R)-5,6-dimethyl-9-((1-methylpyrrolidin-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

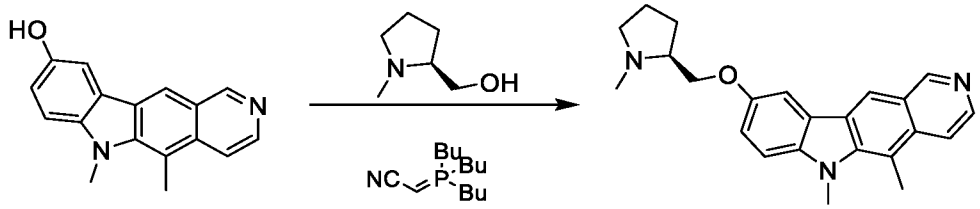


[00140] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 eq) in Tol. (2 mL) was added [(2R)-1-methylpyrrolidin-2-yl]methanol (21.9 mg, 190.6 umol, 22.6 uL, 1 eq) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (92.0 mg, 381.2 umol, 2 eq). The mixture was stirred at 100°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%,9min) to give (R)-5,6-dimethyl-9-((1-methylpyrrolidin-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 360.1 $[M+H]^+$

EXAMPLE 37

(S)-5,6-dimethyl-9-((1-methylpyrrolidin-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

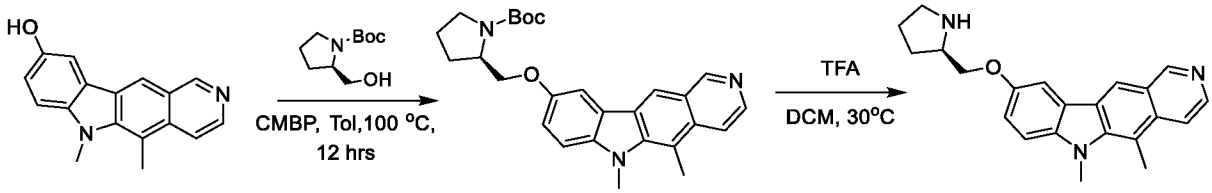


[00141] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 eq) in toluene (2 mL) was added (S)-(1-methylpyrrolidin-2-yl)methanol (21.9 mg, 190.6 umol, 22.6 uL, 1 eq) and 2-(tributylphosphoranylidene)acetonitrile (92.0 mg, 381.2 umol, 2 eq). The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Synergi C18 150*25*10um;mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-35%, 8 min) to afford (S)-5,6-dimethyl-9-((1-methylpyrrolidin-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 360.1 $[M+H]^+$

EXAMPLE 38

(R)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole



Step 1: (R)-tert-butyl2-(((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)-pyrrolidine-1-carboxylate

[00142] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 eq) in Tol. (7 mL) was added tert-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (76.7 mg, 381.2 umol, 1 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (184.0 mg, 762.4 umol, 2 eq). The mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 12 hrs under N_2 atmosphere. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether / Ethyl acetate = 0/1) to give (R)-tert-butyl 2-(((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate.

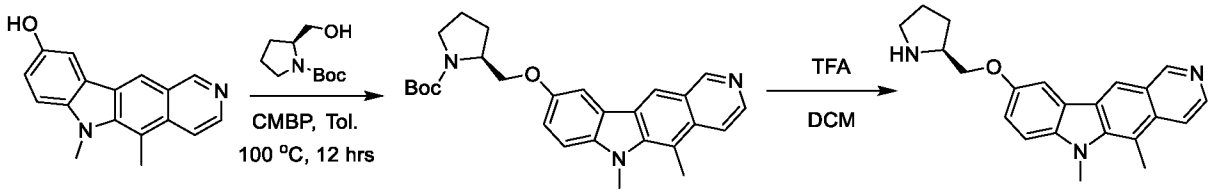
Step 2: (R)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole

[00143] To a solution of (R)-tert-butyl 2-(((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate (150 mg, 336.6 umol, 1 eq) in DCM (3 mL) was added TFA (767.7 mg, 6.7 mmol, 498.5 uL, 20 eq). The mixture was stirred at 30°C 1 hr. LC-MS showed most desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition ; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,8min) to give (R)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 346.1 $[M+H]^+$

EXAMPLE 39

(S)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole



Step 1: (S)-tert-butyl2-(((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)-pyrrolidine-1-carboxylate

[00144] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (100 mg, 380.8 umol, 1 eq) in Tol. (0.5 mL) was added tert-butyl (2S)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (84.3 mg, 418.9 umol, 1.1 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (110.3 mg, 457.0 umol, 1.2 eq). The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO2, DCM: MeOH=10:1) to give (S)-tert-butyl 2-(((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate.

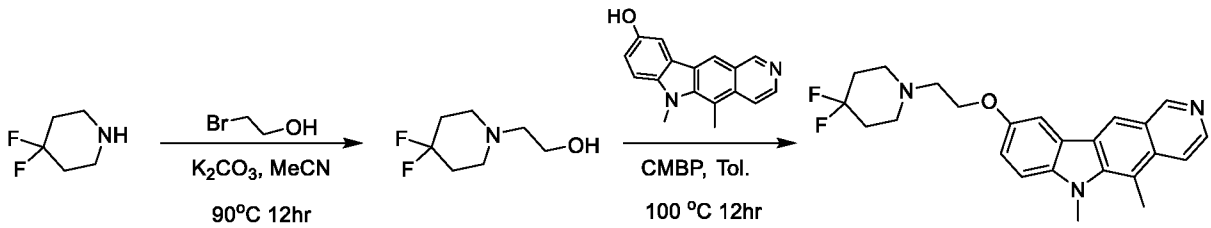
Step 2: (S)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole

[00145] To a solution of tert-butyl (2S)-2-[(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxymethyl]pyrrolidine-1-carboxylate (190 mg, 426.4 umol, 1 eq) in DCM (2 mL) was added TFA (770.0 mg, 6.7 mmol, 0.5 mL, 15.8 eq) .The mixture was stirred at 20°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-45%,8min) to give (S)-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 346.1 $[M+H]^+$

EXAMPLE 40

[00146] 9-(2-(4,4-difluoropiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole



Step 1: 2-(4,4-difluoropiperidin-1-yl)ethanol

[00147] To a solution of 4,4-difluoropiperidine (500 mg, 4.1 mmol, 1 eq), 2-bromoethanol (491.2 mg, 3.9 mmol, 279.1 uL, 1 eq) and K_2CO_3 (461.8 mg, 3.3 mmol, 0.8 eq) in MeCN (20 mL) was heated at 90°C for 12 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was taken in DCM 30 mL, filtered off, and the filtrate concentrated to give 2-(4,4-difluoro-1-piperidyl)ethanol.

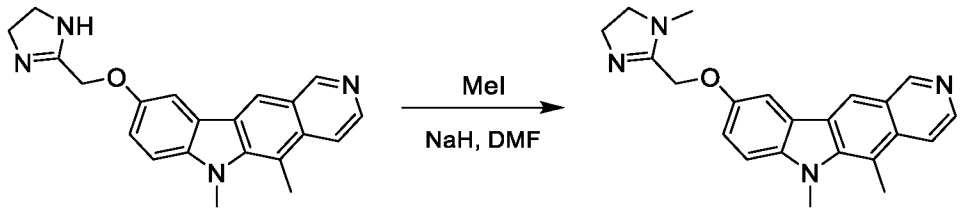
Step 2: 9-(2-(4,4-difluoropiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00148] A mixture of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 eq), 2-(4,4-difluoro-1 -piperidyl)ethanol (75.5 mg, 457.4 umol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene) acetonitrile (184 mg, 762.4 umol, 2 eq) in toluene (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100°C for 12 hrs under N_2 atmosphere. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition ; 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN]; B%: 5%-50%,9min) to give 9-[2-(4,4-difluoro-1-piperidyl)ethoxy]-5,6-dimethyl -pyrido[4,3-b]carbazole.

MS (ESI): m/z = 410.1 $[M+H]^+$

EXAMPLE 41

5,6-dimethyl-9-((1-methyl-4,5-dihydro-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

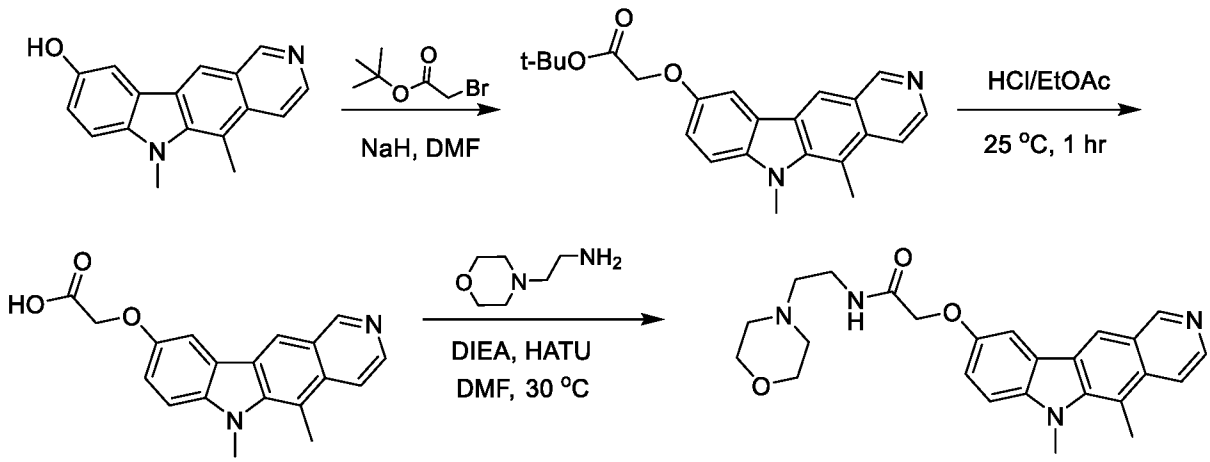


[00149] To a solution of 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-5,6-dimethyl-pyrido[4,3-b] carbazole (50 mg, 109.0 umol, 1 eq, TFA) in DMF (2 mL) was added NaH (13.0 mg, 327.2 umol, 60% purity, 3 eq) at 0°C. The mixture was stirred at 0°C for 0.5 hr. A solution of MeI (15.4 mg, 109.0 umol, 6.7 uL, 1 eq) in DMF (0.5 mL) was added. The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 18%-38%, 8 min) to afford 5,6-dimethyl-9-((1-methyl-4,5-dihydro-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 359.1 $[M+H]^+$

EXAMPLE 42

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-morpholinoethyl)acetamide



Step 1: tert-butyl 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetate

[00150] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (200 mg, 762.4 umol, 1 eq) in THF (5 mL) was added NaH (45.7 mg, 1.1 mmol, 60% purity, 1.5 eq) at 0°C. The mixture was stirred for 0.5 hr. Tert-butyl 2-bromoacetate (178.4 mg, 914.9 umol, 135.2 uL, 1.2 eq) was added and the mixture was stirred at 25°C for 12hr. LCMS showed some desired product was formed. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=0/1) to give tert-butyl 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetate.

Step 2: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetic acid

[00151] A solution of tert-butyl 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetate (75 mg, 199.2 umol, 1 eq) in HCl/EtOAc (2 mL) (4M) was stirred at 25°C for 1 hr. LCMS showed the reaction was completely. The reaction was concentrated to give the crude product of 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetic acid.

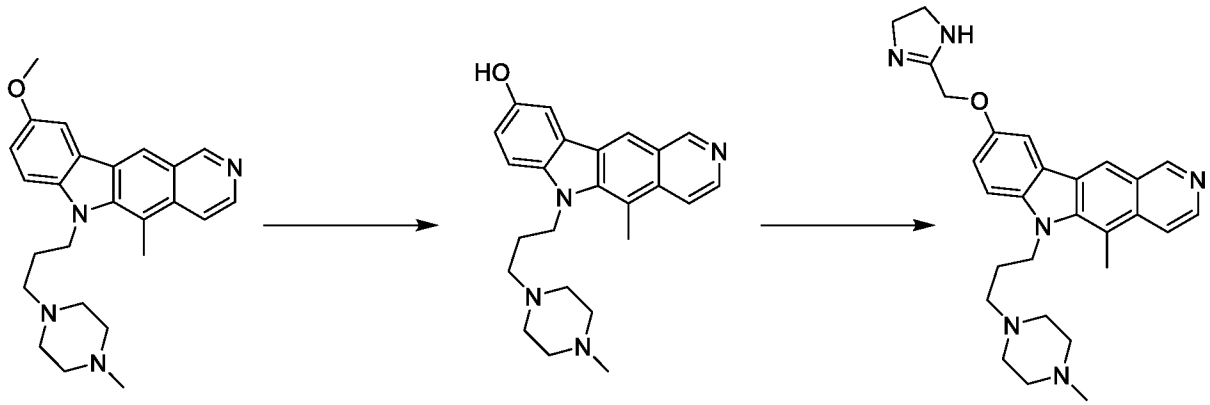
Step 3: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-morpholinoethyl)-acetamide

[00152] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (30 mg, 84.0 umol, 1 eq, HCl) in DMF (2 mL) was added DIEA (27.1 mg, 210.2 umol, 36.6 uL, 2.5 eq), HATU (47.9 mg, 126.1 umol, 1.5 eq) and 2-morpholinoethanamine (12.0 mg, 92.4 umol, 12.1 uL, 1.1 eq). The mixture was stirred at 30°C for 12 hr. LCMS showed some desired product was formed. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-45%, 8 min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-morpholinoethyl)acetamide.

MS (ESI): m/z = 433.1 $[M+H]^+$

EXAMPLE 43

9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6-(3-(4-methylpiperazin-1-yl)propyl)-6H-pyrido[4,3-b]carbazole



Step 1: 9-hydroxy-5-methyl-6-(3-(4-methylpiperazin-1-yl)propyl)-6H-pyrido[4,3-b]carbazole

[00153] To a solution of 9-methoxy-5-methyl-6-(3-(4-methylpiperazin-1-yl)propyl)-6H-pyrido[4,3-b]carbazole (20 mg, 0.05 mmol) in DCM (0.5 ml) was added BBr_3 (23 uL, 0.25 mmol) and the mixture was stirred at rt overnight, then added NH_4OH aq and DCM/MeOH (10:1). The org phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the title compound.

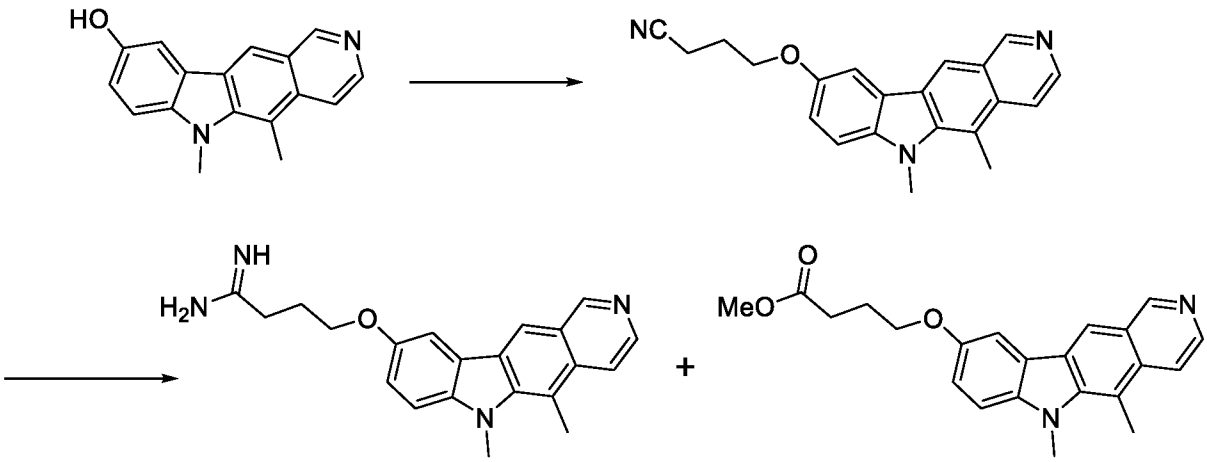
Step 2: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6-(3-(4-methylpiperazin-1-yl)propyl)-6H-pyrido[4,3-b]carbazole

[00154] To a solution of the product of step 1 (14 mg, 0.036 mmol) in THF (1 ml) was added NaI (5 mg, 0.036 mmol), KOt-Bu (8 mg, 0.072 mmol) and alkyl chloride (10 mg, 0.072 mmol) and the mixture was heated at 70 °C for 6 h, then purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the title compound.

MS (ESI): 471.3 [M+H]+

EXAMPLE 44

4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butanimidamide (44a) & methyl 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butanoate (44b)



Step 1: 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butyronitrile

[00155] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (26 mg, 0.10 mmol) in THF was added NaI (15 mg, 0.1 mmol), KOtBu (17 mg, 0.15 mmol) and chlorobutyronitrile (31 mg, 0.3 mmol) and the mixture was stirred at 70 °C overnight and then purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the title compound.

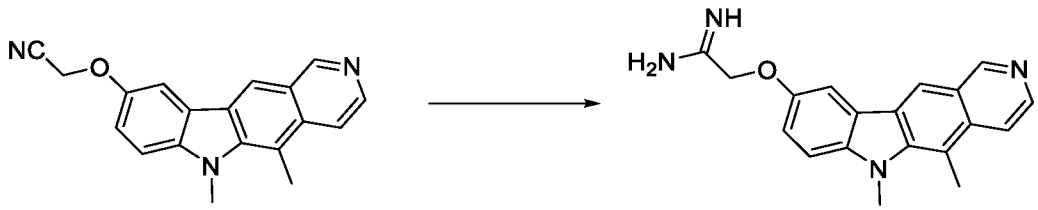
Step 2: 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butanimidamide (44a) & methyl 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butanoate (44b)

[00156] To a solution of the product of Step 1 (21 mg, 0.64 mmol) in MeOH was added AcCl (0.2 ml) and the mixture was stirred for 6 h at rt, then the volatile was removed and then NH4OH aq (1 ml) was added and stirred at rt overnight. The resulting mixture was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford compound 44a and compound 44b.

44a: MS (ESI): 347.2 [M+H]+; **44b:** MS (ESI): 363.2 [M+H]+

EXAMPLE 45

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetimidamide

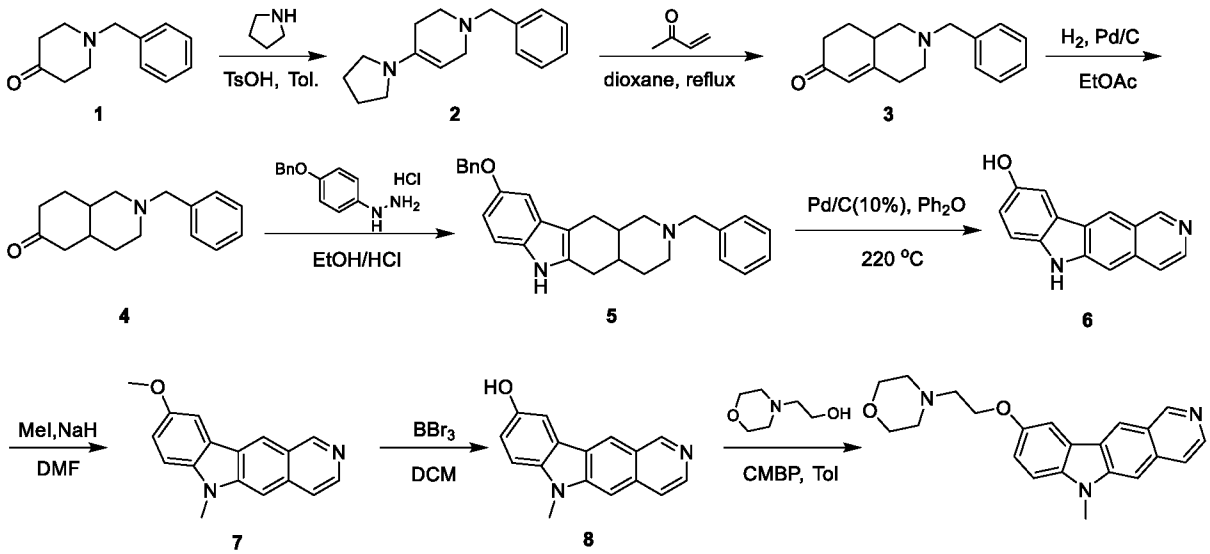


[00157] To a solution of 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetonitrile (13 mg, 0.043 mmol) in MeOH was added AcCl (0.2 ml) at rt overnight, then the volatile was removed. The residue was added NH4OH aq (1 ml) and the mixture was stirred for 3h at rt and purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the title compound.

MS (ESI): 319.2 [M+H]+

EXAMPLE 46

[00158] 4-[2-(6-methylpyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine



Step 1: 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine

[00159] A mixture of 1-benzylpiperidin-4-one (50 g, 264.20 mmol, 49.02 mL, 1 eq), pyrrolidine (56.3 g, 792.5 mmol, 66.1 mL, 3 eq), 4-methylbenzenesulfonic acid (4.5 g, 26.4 mmol, 0.1 eq), in 100 mL of toluene was stirred at 110°C for 1hr. TLC showed the reaction

was completed. The reaction mixture was filtered and concentrated under reduced pressure to give 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine.

Step 2: 2-benzyl-1,3,4,7,8,8a-hexahydroisoquinolin-6(2H)-one

[00160] To a solution of 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine (40 g, 165.04 mmol, 1 eq) in dioxane (300.0 mL) was added but-3-en-2-one (12.7 g, 181.5 mmol, 15.1 mL, 1.1 eq). The mixture was stirred at 100°C for 12hr. LCMS showed the reaction was completed. The reaction mixture was quenched by addition 60 mL HCl(10%), and then diluted with 500 mL of H_2O and extracted with 1000 mL of ethyl acetate. The combined organic layers were washed with 500 mL of brine, 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 = 1/0 to 0/1) to give 2-benzyl-1,3,4,7,8,8a- hexahydroisoquinolin-6(2H)-one.

Step 3: 2-benzyl-1,3,4,4a,5,7,8,8a-octahydroisoquinolin-6-one

[00161] To a solution of 2-benzyl-1,3,4,7,8,8a-hexahydroisoquinolin-6-one (9 g, 37.2 mmol, 1 eq) in 50 mL of ethyl acetate was added Pd/C (1 g, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (15Psi) at 20°C for 0.5hr. LCMS showed the 2-benzyl-1,3,4,7,8,8a-hexahydroisoquinolin-6-one remained, and then the mixture was stirred at 20°C for another 2 hr. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give 2-benzyl-1,3,4,4a,5,7,8,8a-octahydroisoquinolin-6-one.

Step 4: 2-benzyl-9-benzyloxy-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-b]carbazole

[00162] A mixture of 2-benzyl-1,3,4,4a,5,7,8,8a-octahydroisoquinolin-6-one (18 g, 73.9 mmol, 1 eq), (4-benzyloxyphenyl)hydrazine;hydrochloride (21.2 g, 73.9 mmol, 1 eq, HCl), HCl (12 M, 4.00 mL, 6.49e-1 eq), in 200 mL of EtOH was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 20°C for 12 hr under N_2 atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition 500 mL of sat.$NaHCO_3$, and extracted with 1000 mL of ethyl acetate. The combined organic layers were washed with 500 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (basic condition, column: Agela DuraShell C18 250*70mm*10um; mobile phase: [water(0.05%NH_3H_2O+10mMNH_4HCO_3)-ACN];B%: 70%-95%,20min) to give 2-bezyl-9-benzyloxy-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-b]carbazole.

Step 5: 6H-pyrido[4,3-b]carbazol-9-ol

[00163] A mixture of 2-benzyl-9-benzyloxy-1,3,4,4a,5,6,11,11a-octahydropyrido[4,3-b]carbazole (600 mg, 1.4 mmol, 1 eq) and Pd/C (300 mg, 10% purity) in 10 mL of diphenyl ether, and then the mixture was stirred at 250°C for 30min. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give 6H-pyrido[4,3-b]carbazol-9-ol.

Step 6: 9-methoxy-6-methyl-pyrido[4,3-b]carbazole

[00164] To a solution of 6H-pyrido[4,3-b]carbazol-9-ol (80 mg, 341.51 µmol, 1 eq) in 1 mL of DMF was added NaH (27.32 mg, 683.02 µmol, 60% purity, 2 eq) at 0°C. The mixture was stirred a 0°C for 0.5 hr, then MeI (96.9 mg, 683.0 µmol, 2 eq) in 0.1 mL of DMF was added to above solution at 0°C, then the mixture was stirred 20°C for 0.5hr. LCMS showed the reaction was completed. The reaction mixture was quenched by addition 30 mL of water at 0°C, extracted with 200 mL of ethyl acetate. The combined organic layers were washed with 50 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, eluting with Ethyl acetate : Methanol = 10:1) to give 9-methoxy-6-methyl-pyrido[4,3-b]carbazole.

Step 7: 6-methylpyrido[4,3-b]carbazol-9-ol

[00165] To a solution of 9-methoxy-6-methyl-pyrido[4,3-b]carbazole (70 mg, 266.86 µmol, 1 eq) in 3 mL of DCM was added BBr_3 (133.71 mg, 533.73 µmol, 2 eq) at 0°C .The mixture was stirred at 0°C for 1 hr. LCMS showed the reaction was completed. The reaction mixture was poured into 10 mL of sat.$NaHCO_3$ at 0 °C, and then diluted with 30 mL of H_2O and extracted with 100 mL of ethyl acetate. The combined organic layers were washed with 200 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-methylpyrido[4,3-b]carbazol-9-ol.

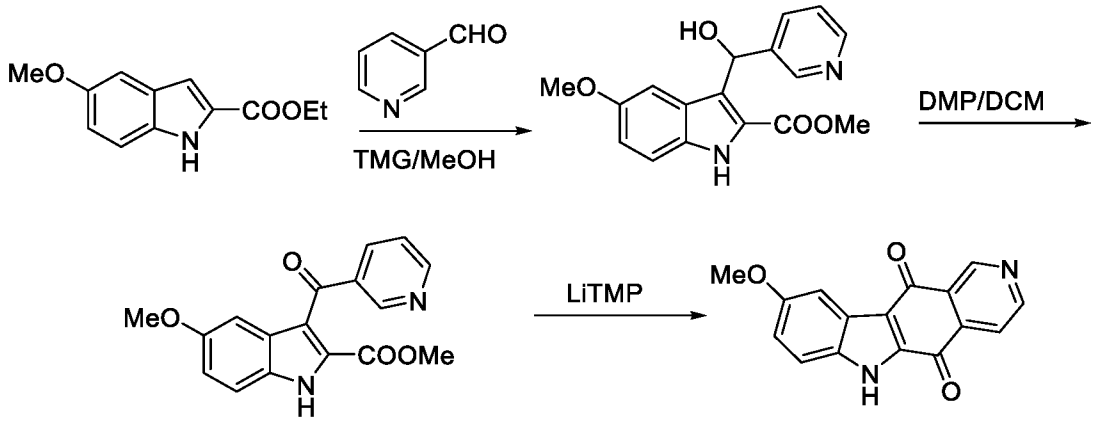
Step 8: 4-[2-(6-methylpyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine

[00166] A mixture of 2-morpholinoethanol (39.6 mg, 302.0 µmol, 1.5 eq), 6-methylpyrido [4,3-b]carbazol-9-ol (50 mg, 201.3 µmol, 1 eq), 2-(tributyl-λ^5-phosphanylidene)acetonitrile (72.9 mg, 302.0 µmol, 1.5 eq), in 3 mL of toluene and then the mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition, column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(0.2%FA)-ACN];B%: 1%-45%,8min) to give 4-[2-(6-methylpyrido[4,3-b carbazol-9-yl)oxyethyl]morpholine.

MS (ESI): m/z = 362.1 $[M+H]^+$

EXAMPLE 47

[00167] 9-methoxy-5H-pyrido[4,3-b]carbazole-5,11(6H)-dione



Step 1: methyl 3-(hydroxy(pyridin-3-yl)methyl)-5-methoxy-1H-indole-2-carboxylate

[00168] To a solution of ethyl 5-methoxyindolecarboxylate (2.2 g, 10.0 mmol) in DCM (50 ml) was added AlCl3 (2.66 g, 20 mmol) and stirred at rt for 30 min and cooled to 0 °C, added 3-pyridinecarbaldehyde (2.1 g, 20 mmol). The mixture was slowly warmed to rt and stirred overnight at rt (observed a big chunk). The mixture was quenched with water and the aq phase was extracted with EtOAc (2 times). The combined org phase was washed with brine and dried over Na2SO4 and concentrated in vacuo. The residue was purified with column chromatography (Hexanes: EtOAc = 0 to 100%) to afford the title compound methyl 3-(hydroxy(pyridin-3-yl)methyl)-5-methoxy-1H-indole-2-carboxylate which was used in next step.

Step 2: methyl 5-methoxy-3-nicotinoyl-1H-indole-2-carboxylate

[00169] To a solution of methyl 3-(hydroxy(pyridin-3-yl)methyl)-5-methoxy-1H-indole-2-carboxylate in DCM (67 ml) was added DMP (2.8 g, 6.7 mmol) at 0 °C and warmed to rt. The mixture was stirred for 1 h and added NaHCO3 aq and Na2S2O5, EtOAc. The org phase was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was purified with column chromatography (Hexanes: EtOAc = 0 to 100%) to afford the desired product.

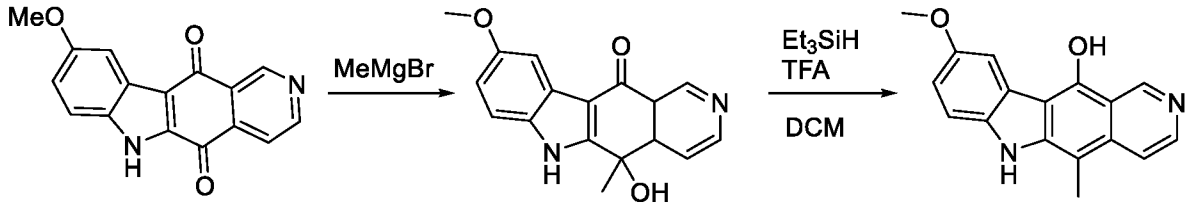
Step 3: 9-methoxy-5H-pyrido[4,3-b]carbazole-5,11(6H)-dione

[00170] To a solution of tetramethylpiperidine (7.2 ml, 45.0 mmol) in THF (15 ml) was added n-BuLi (2.5M, 18 ml, 40 mmol) at 0 °C and stirred for 15 min. The mixture was cooled to -78 °C and added 5-methoxy-3-nicotinoyl-1H-indole-2-carboxylate (3.0 g, 9.2 mmol) in 15 ml of THF and stirred for 3 h, then quenched with water and added 200 ml of hexanes and 200 ml of sat NaHCO3 aq. The suspension was filtered over disposable 10 Micron

Polyethylene Frit (required 8 of them since it get clogged) and washed with water and EtOAc to remove impurity. The residue was dried under high vac overnight to provide the title compound

EXAMPLE 48

9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-11-ol



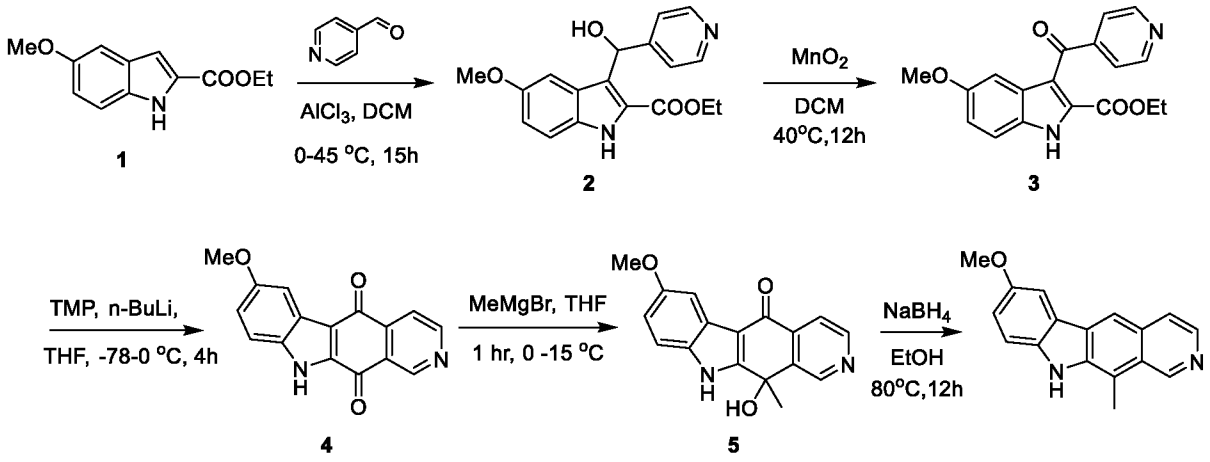
[00171] To a solution of 9-methoxy-5H-pyrido[4,3-b]carbazole-5,11(6H)-dione (120 mg, 0.43 mmol) in THF (5 ml) was added MeMgBr (1 ml, 3.0 mmol) at 0 °C, and stirred at rt and stirred for 1 h, then added with NH4Cl aq and EtOAc. The org phase was washed with NaHCO3 aq and brine, dried over Na2SO4 and concentrated in vacuo.

[00172] The residue was dissolved in DCM (1 ml) then TFA (0.1 ml) and triethyl silane (0.1 ml) were added and the mixture was stirred overnight at rt. The volatiles were removed and the residue purified with RP-HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the title compound.

MS (ESI): 279.2 [M+H]+

EXAMPLE 49

7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazole



Step 1: ethyl 3-(hydroxy(pyridin-4-yl)methyl)-5-methoxy-1H-indole-2-carboxylate

[00173] To a solution of pyridine-4-carbaldehyde (1.9 g, 18.2 mmol, 1.7 mL, 2 eq) in DCM (30 mL) was added $AlCl_3$ (2.4 g, 18.2 mmol, 997.0 uL, 2 eq), and the mixture was stirred at 20°C for 30 min under N_2. then ethyl 5-methoxy-1H-indole-2-carboxylate (2.0 g, 9.1 mmol, 1 eq) was added to the mixture at 0°C, which was brought back to 20°C and stirred for 3 hrs. LC-MS showed Reactant 1 was not consumed completely then the reaction was stirred at 45°C for 12 hrs. LC-MS showed Reactant 1 was consumed and desired mass was detected. The mixture was then quenched with ice cold water (100 mL) and extracted with DCM (3 × 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give solid material. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient @ 70 mL/min) to give ethyl 3-[hydroxy(4-pyridyl)methyl]-5-methoxy-1H-indole-2-carboxylate.

Step 2: ethyl 3-isonicotinoyl-5-methoxy-1H-indole-2-carboxylate

[00174] To a solution of ethyl 3-[hydroxy(4-pyridyl)methyl]-5-methoxy-1H-indole-2-carboxylate (0.9 g, 2.7 mmol, 1 eq) in DCM (30 mL) was added MnO_2 (4.8 g, 55.1 mmol, 20 eq). The mixture was stirred at 40°C for 12 hrs. LC-MS showed ethyl 3-[hydroxy(4-pyridyl)methyl]-5-methoxy-1H-indole-2-carboxylate was consumed and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give ethyl 5-methoxy-3-(pyridine-4-carbonyl)-1H-indole -2-carboxylate.

Step 3: 7-methoxy-10H-pyrido[3,4-b] carbazole-5,11-dione

[00175] To a solution of TMP (979.9 mg, 6.9 mmol, 1.1 mL, 5 eq) in THF (15 mL) was added n-BuLi (2.5 M, 2.4 mL, 4.3 eq) at 0°C and stirred for 1 hr. The mixture was cooled to -78°C and added ethyl 5-methoxy-3-(pyridine-4-carbonyl)-1H-indole-2-carboxylate (0.4 g, 1.3 mmol, 1 eq) in THF (5 mL) and stirred for 3 hrs at -78°C. LC-MS showed ethyl 5-methoxy-3-(pyridine-4-carbonyl)-1H-indole-2-carboxylate was consumed and desired mass was detected. The reaction mixture was quenched by addition NH_4Cl 50 mL, and extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine (50 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 70 mL/min) to give 7-methoxy-10H-pyrido[3,4-b] carbazole-5,11-dione.

Step 4: 11-hydroxy-7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazol-5-one

[00176] To a solution of 7-methoxy-10H-pyrido[3,4-b]carbazole-5,11-dione (120 mg, 431.2 umol, 1 eq) in THF (4 mL) was added bromo(methyl)magnesium (3 M, 316.2 uL, 2.2

eq) at 0°C. The mixture was stirred at 15°C for 1hr. TLC indicated 7-methoxy-10H-pyrido[3,4-b] carbazole-5,11-dione was consumed completely and one new spot formed. The reaction was added to saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give 11-hydroxy-7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazol-5-one.

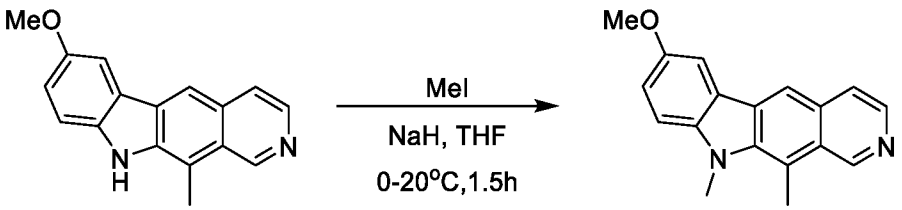
Step 5: 7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazole

[00177] To a solution of 11-hydroxy-7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazol-5-one (120 mg, 407.7 umol, 1 eq) in EtOH (3 mL) was added $NaBH_4$ (107.9 mg, 2.8 mmol, 7 eq). The mixture was stirred at 80°C for 12 hrs. LC-MS showed 11-hydroxy-7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazol-5-one was consumed and desired mass was detected. The reaction was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (5 mL × 3). The combined organic phase was washed with brine (10 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=0:1) and then the residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 30%-60%,9min) to afford 7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazole

MS (ESI): m/z = 263.0 $[M+H]^+$

EXAMPLE 50

7-methoxy-10,11-dimethyl-10H-pyrido[3,4-b]carbazole



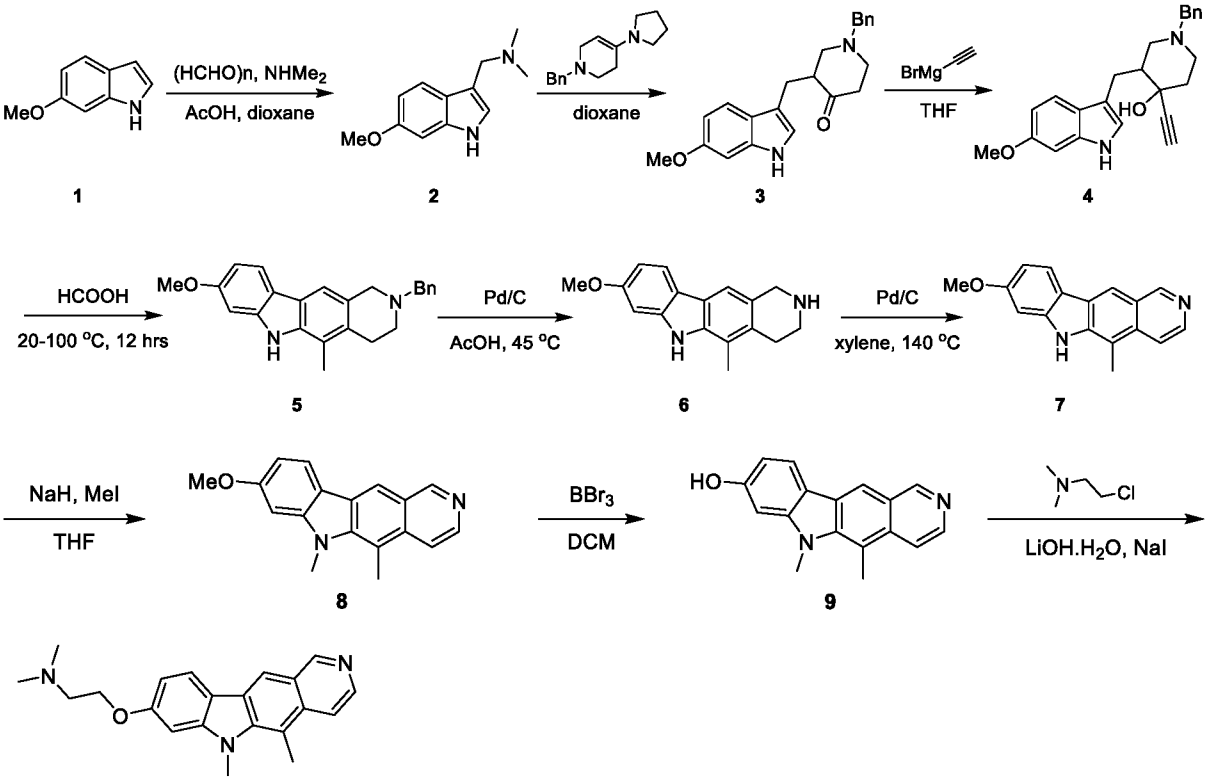
[00178] To a solution of 7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazole (40 mg, 106.2 umol, 1 eq, TFA) in THF (4 mL) was added NaH (12.7 mg, 318.8 umol, 60% purity, 3 eq) was stirred at 0°C, then the reaction was stirred at 20°C for 30 min, then MeI (18.1 mg, 127.5 umol, 7.9 uL, 1.2 eq) was added at 20°C. The mixture was stirred at 20°C for 1 hr. LC-MS showed 7-methoxy-11-methyl-10H-pyrido[3,4-b]carbazole was consumed and desired mass was detected. The reaction mixture was quenched by addition NH_4Cl 5 mL, and then diluted with water 5 mL and extracted with Ethyl acetate (5 mL × 3). The combined organic layers were washed with brine (5 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-

HPLC (FA condition; column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 15%-45%,10min) to give 7-methoxy-10,11-dimethyl-pyrido[3,4-b]carbazole.

MS (ESI): m/z = 277.1 $[M+H]^+$

EXAMPLE 51

[00179] 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-yl)oxy)-N,N-dimethylethanamine



Step 1: 1-(6-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[00180] To a stirred solution of 6-methoxy-1H-indole (5 g, 33.9 mmol, 1 eq) and N-methylmethanamine;hydrochloride (3.0 g, 37.3 mmol, 1.1 eq) in dioxane (30 mL) and H_2O (30 mL) was added formaldehyde (3.0 g, 37.3 mmol, 2.7 mL, 37% purity, 1.1 eq), TEA (3.7 g, 37.3 mmol, 5.2 mL, 1.1 eq) and AcOH (3.0 g, 50.9 mmol, 2.9 mL, 1.5 eq) at 20°C. The reaction mixture was stirred at 20°C for 12 hr. LC-MS showed 6-methoxy-1H-indole was consumed completely and about 68.9% of desired compound was detected. The reaction mixture was concentrated to give a residue. The residue was adjusted to pH 12 with 2M NaOH solution and filtered. The cake was dried to afford the crude product of 1-(6-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine.

Step 2: 1-benzyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[00181] To a stirred solution of 1-(6-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine (3 g, 14.6 mmol, 1 eq) in dioxane (60 mL) was added 1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine (8.9 g, 36.7 mmol, 2.5 eq) at 20°C, the reaction mixture was stirred at 120°C for 12 hr. TLC (Petroleum ether/Ethyl acetate = 1/1, Rf = 0.35) and LCMS indicated 1-(6-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine was consumed completely and one new spot formed. After cooling to 20°C, the reaction mixture was concentrated. The residue was diluted with water (50 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (50 mL × 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography plate 1 (SiO_2, Petroleum ether/Ethyl acetate=1/0 to 1/1) (Petroleum ether/Ethyl acetate = 1/1, Rf = 0.35) to give 1-benzyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-one.

Step 3: 1-benzyl-4-ethynyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[00182] To a stirred solution of 1-benzyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-one (4.4 g, 12.6 mmol, 1 eq) in THF (50 mL) was added bromo(ethynyl)magnesium (0.5 M, 75.7 mL, 3 eq) dropwise at 0°C, the reaction mixture was stirred at 0°C for 3 hr under N_2. TLC (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.43) indicated -benzyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-one was consumed completely and one new spot formed. The reaction mixture was poured into ice saturated NH_4Cl solution (50 mL) and the aqueous phase was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (50 mL × 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford 1-benzyl-4-ethynyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol.

Step 4: 2-benzyl-8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00183] 1-benzyl-4-ethynyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (5 g, 13.3 mmol, 1 eq) was dissolved into formic acid (30 mL) at 20°C and the reaction mixture was stirred at 100°C for 12 hr. LC-MS showed 1-benzyl-4-ethynyl-3-((6-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol was consumed completely and about 55% of desired compound was detected. After cooling to 20°C, the reaction mixture was concentrated. The residue was diluted with ethyl acetate (50 mL) and adjusted to pH 8 with saturated $NaHCO_3$ solution. The aqueous phase was extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (50 mL × 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2, Petroleum ether/(Ethyl acetate/Ethanol = 3/1) = 1/0 to 1/1) (Petroleum ether/(Ethyl acetate/Ethanol = 3/1) = 1/1, Rf = 0.70) to afford 2-benzyl-8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 5: 8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00184] To a solution of 2-benzyl-8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (1 g, 2.8 mmol, 1 eq) in AcOH (5 mL) was added Pd/C (500 mg, 10% purity) at 20°C under N_2. The suspension was degassed under vacuum and purged with H_2 for 3 times. The mixture was stirred under H_2 (15psi) at 45°C for 2 hr. LC-MS showed 2-benzyl-8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole was consumed completely and about 45.5% of desired compound was detected. After cooling to 20°C, the reaction mixture was filtered and the filtrate was concentrated. The residue was triturated with ethyl acetate (5 mL) at 20 °C for 15 min to afford 8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 6: 8-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00185] To a stirred solution of Pd/C (500 mg, 10% purity) in xylene (10 mL) was added 8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (500 mg, 1.8 mmol, 1 eq) at 20°C, the reaction mixture was stirred at 140°C for 12 hr. LCMS showed 8-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole was consumed completely and about 94.5% of desired compound was detected. After cooling to 20°C, the reaction mixture was diluted with methanol (20 mL) and filtered through Celite. The filtrate was concentrated to give 8-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

Step 7: 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00186] To a stirred solution of 8-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (320 mg, 1.2 mmol, 1 eq) in THF (5 mL) was added NaH (146.3 mg, 3.6 mmol, 60% purity, 3 eq) at 0°C, the reaction mixture was stirred at 0°C for 1 hr. Then MeI (155.8 mg, 1.1 mmol, 68.3 uL, 0.9 eq) was added and the reaction mixture was warmed to 20°C and stirred for 2 hr. LCMS showed 8-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole was consumed completely and about 79% of desired compound was detected. The reaction mixture was poured into ice saturated NH_4Cl solution (3 mL). The aqueous phase was extracted with ethyl acetate (3 mL × 4). The combined organic phase was washed with brine (3 mL × 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to afford 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

Step 8: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-ol

[00187] To a stirred solution of 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (430 mg, 1.5 mmol, 1 eq) in DCM (10 mL) was added BBr_3 (1.9 g, 7.7 mmol, 749.6 uL, 5 eq) at 0°C, the reaction mixture was stirred at 45°C for 1 hr under N_2. LCMS showed 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole was consumed completely and about 82%

of desired compound was detected. After cooling to 20°C, the reaction mixture was poured into ice saturated $NaHCO_3$ solution (20 mL) and adjusted to pH 8 with $NaHCO_3$ solid. The mixture was concentrated under reduced pressure to remove DCM and filtered. The cake was washed with water (10 mL) and dried to afford 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-ol.

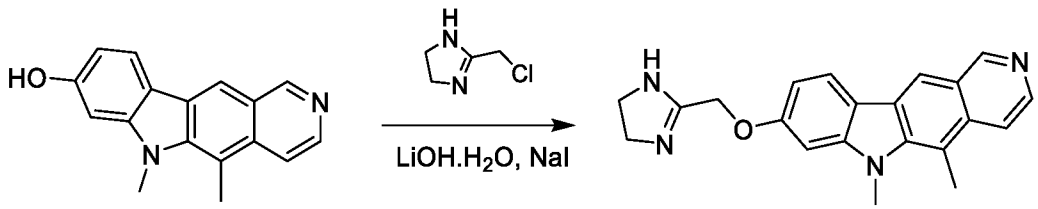
Step 9: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-yl)oxy)-N,N-dimethylethanamine

[00188] To a stirred solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-ol (50 mg, 190.6 umol, 1 eq) and 2-chloro-N,N-dimethyl-ethanamine (32.9 mg, 228.7 umol, 1.2 eq, HCl) in DMF (2 mL) was added $LiOH.H_2O$ (31.9 mg, 762.4 umol, 4 eq) and NaI (28.5 mg, 190.6 umol, 1 eq) at 20°C, the reaction mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-40%, 9 min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-yl)oxy)-N,N-dimethylethanamine.

MS (ESI): m/z = 334.1 $[M+H]^+$

EXAMPLE 52

8-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

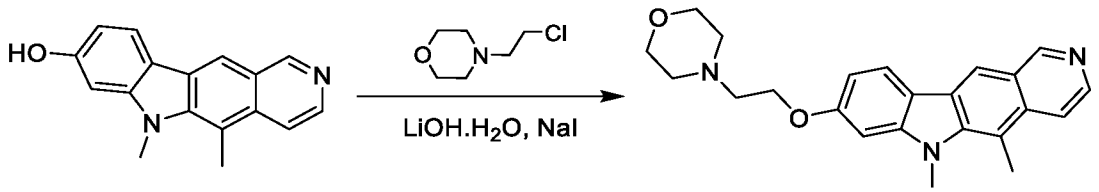


[00189] To a stirred solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-ol (50 mg, 190.6 umol, 1 eq) and 2-(chloromethyl)-4,5-dihydro-1H-imidazole (35.4 mg, 228.7 umol, 1.2 eq, HCl) in DMF (4 mL) was added $LiOH.H_2O$ (31.9 mg, 762.4 umol, 4 eq) and NaI (28.5 mg, 190.6 umol, 1 eq) at 20°C, the reaction mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-40%, 9 min) to afford 8-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 345.1 $[M+H]^+$

EXAMPLE 53

4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-yl)oxy)ethyl)morpholine

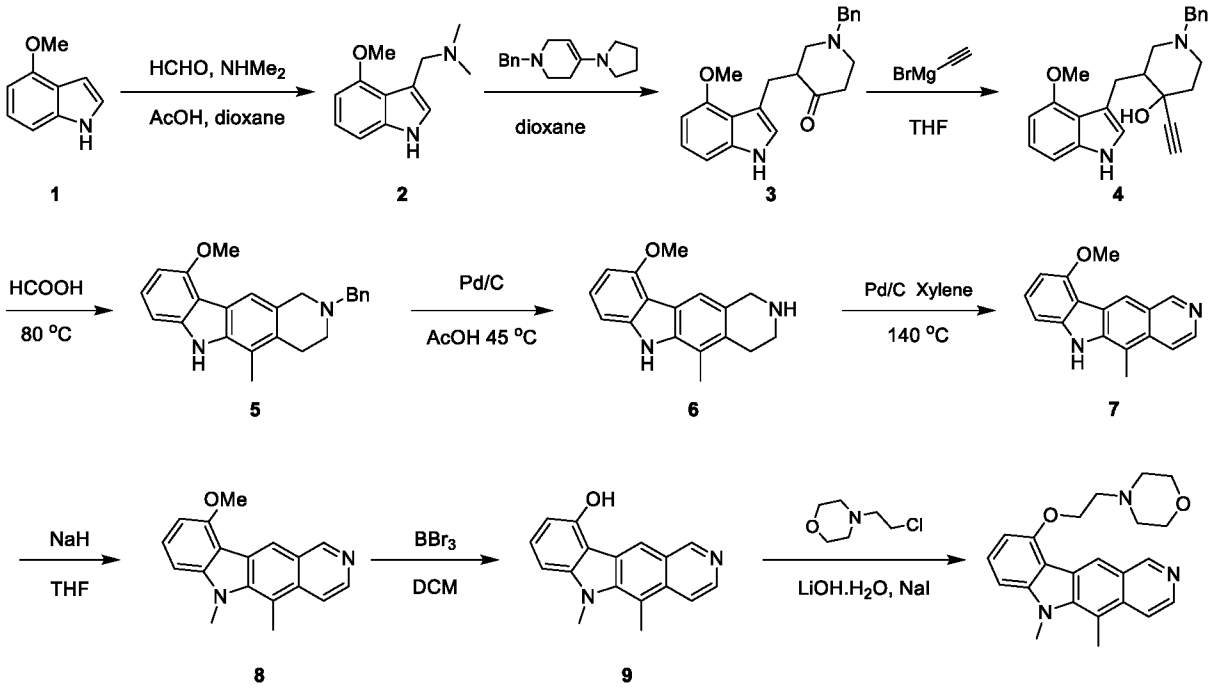


[00190] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-10-ol (50.3 mg, 192.0 umol, 1 eq) in DMF (4 mL) was added 4-(2-chloroethyl)morpholine (42.8 mg, 230.4 umol, 1.2 eq, HCl), $LiOH.H_2O$ (32.2 mg, 768.2 umol, 4 eq) and NaI (28.7 mg, 192.0 umol, 1 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 250*50mm*10 um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,10min) to give 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-8-yl)oxy)ethyl)morpholine.

MS (ESI): m/z = 376.1 $[M+H]^+$

EXAMPLE 54

4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-yl)oxy)ethyl)morpholine



Step 1: 1-(4-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[00191] To a solution of N-methylmethanamine;hydrochloride (15.2 g, 129.1 mmol, 0.7 eq, HCl) in dioxane (200 mL) and H_2O (200 mL) was added TEA (18.9 g, 186.8 mmol, 26.0 mL, 1.1 eq), AcOH (15.3 g, 254.8 mmol, 14.5 mL, 1.5 eq), 4-methoxy-1H-indole (25 g, 169.8 mmol, 1 eq) and formaldehyde (15.1 g, 186.8 mmol, 13.9 mL, 37% purity, 1.1 eq).

The mixture was stirred at 20°C for 12 hr. LC-MS showed the desired compound was detected. The mixture was concentrated to remove the dioxane . The reaction was addded to 100mL of NaOH (2M). The reaction mixture was filtered and the filter cake was washed with 300 mL of H_2O, dried in vacuum to give crude 1-(4-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine.

Step 2: 1-benzyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[00192] To a solution of 1-(4-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine (22 g, 107.7 mmol, 1 eq) in dioxane (400 mL) was added 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine (65.2 g, 269.2 mmol, 2.5 eq). The mixture was stirred at 120°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between H_2O 200 mL and EtOAc 200 mL. The aqueous phase was washed with EtOAc (200 mL × 3), The organic phase was separated and washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient @ 100 mL/min) to give 1-benzyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-one.

Step 3: benzyl-4-ethynyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[00193] To a solution of 1-benzyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-one (25 g, 71.7 mmol, 1 eq) in THF (300 mL) was added bromo(ethynyl)magnesium (0.5 M, 430.4 mL, 3 eq). The mixture was stirred at 0°Cfor 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl 300 mL and EtOAc 200 mL. The aqueous phase was washed with EtOAc (500 mL × 3). The organic phase was separated, washed with brine (200 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give benzyl-4-ethynyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol.

Step 4: 2-benzyl-10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00194] HCOOH (300 mL) was added to benzyl-4-ethynyl-3-((4-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (26.8 g, 71.5 mmol, 1 eq). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure. The residue was diluted with $NaHCO_3$ 300 mL and extracted with EtOAc (300 mL × 3). The combined organic layers were washed with brine(150 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient

@ 50 mL/min) to give 2-benzyl-10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 5: 10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00195] A mixture of 2-benzyl-10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (6.5 g, 18.2 mmol, 1 eq), Pd/C (3 g, 561.0 umol, 10% purity) in AcOH (100 mL) was degassed and purged with H_2 (15 psi) for 3 times, and then the mixture was stirred at 45°C for 2 hr under H_2 (15 psi) atmosphere. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give 10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 6: 10-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00196] To a solution of Pd/C (500 mg, 10% purity) in xylene (30 mL) was added 10-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (1 g, 3.7 mmol, 1 eq). The mixture was stirred at 145°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give crude 10-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole.

Step 7: 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00197] To a solution of 10-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (650 mg, 2.4 mmol, 1 eq) in THF (10 mL) was added NaH (297.3 mg, 7.4 mmol, 60% purity, 3 eq) at 0°C and stirred for 30 min, MeI (351.7 mg, 2.4 mmol, 154.2 uL, 1 eq) was added to the mixture at 0°C. The mixture was stirred at 25°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl 100 mL and EtOAc 50 mL. The aqueous phase was washed with EtOAc (50 mL × 3), the organic phase was separated and washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate / Petroleum ether gradient @ 75mL/min) to give 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

Step 8: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-ol

[00198] To a solution of 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (300 mg, 1.0 mmol, 1 eq) in DCM (10 mL) was added BBr_3 (1.3 g, 5.4 mmol, 523.0 uL, 5 eq) at 0°C. The mixture was stirred at 25°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was washed with $NaHCO_3$ (30 mL) and filtered and the filter cake was washed with 20 mL of H_2O, dried in vacuum to give crude 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-ol.

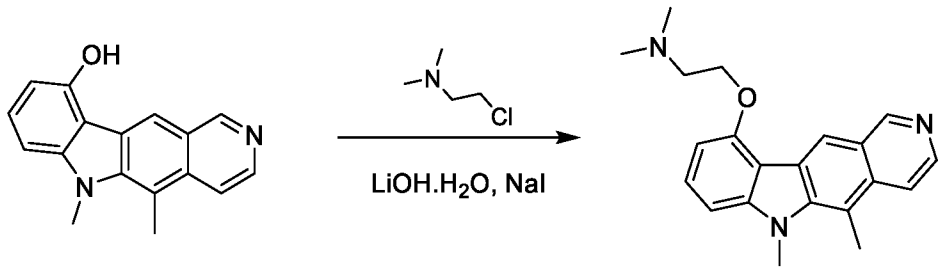
Step 9: 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-yl)oxy)ethyl)morpholine

[00199] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-ol (50 mg, 190.6 umol, 1 eq) in DMF (4 mL) was added 4-(2-chloroethyl)morpholine (42.5 mg, 228.7 umol, 1.2 eq, HCl), NaI (28.5 mg, 190.6 umol, 1 eq) and $LiOH.H_2O$ (32.0 mg, 762.4 umol, 4 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completely. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [water(0.2%FA)-ACN]; B%: 10%-45%, 9 min) to give 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-yl)oxy)ethyl)morpholine.

MS (ESI): m/z = 376.1 $[M+H]^+$

EXAMPLE 55

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-yl)oxy)-N,N-dimethylethanamine

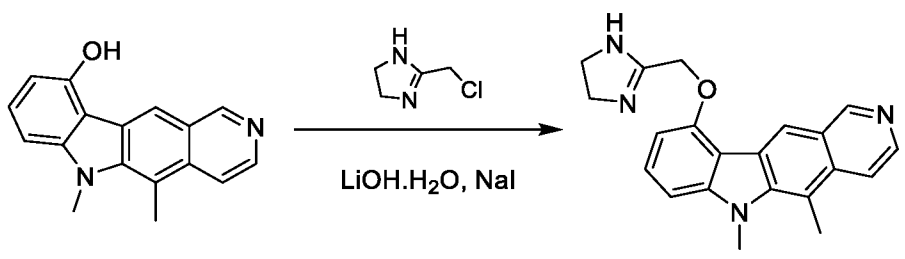


[00200] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-ol (70 mg, 266.8 umol, 1 *eq*) in DMF (4 mL) was added 2-chloro-N,N-dimethyl-ethanamine (34.4 mg, 239.1 umol, 1.2 *eq*, HCl), $LiOH.H_2O$ (44.7 mg, 1.0 mmol, 4 *eq*) and NaI (40.0 mg, 266.8 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate was a crude product. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%,9 min) to give 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-yl)oxy)-N,N-dimethylethanamine.

MS (ESI): m/z = 334.1 $[M+H]^+$

EXAMPLE 56

10-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

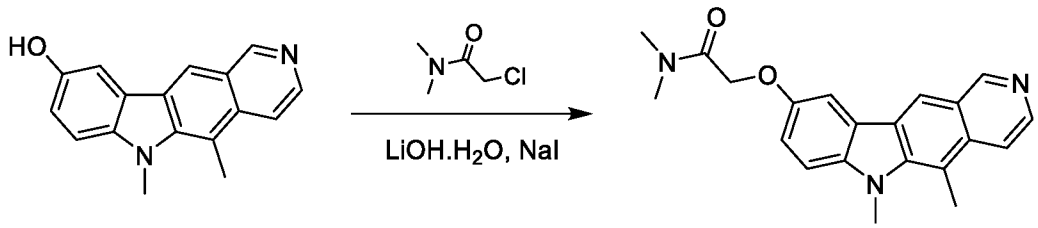


[00201] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-10-ol (50 mg, 190.6 umol, 1 *eq*) in DMF (4 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (35.4 mg, 228.7 umol, 1.2 *eq*, HCl), $LiOH.H_2O$ (31.9 mg, 762.4 umol, 4 *eq*) and NaI (28.5 mg, 190.6 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate to give crude product. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%, 9 min) to give 10-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 345.1 $[M+H]^+$

EXAMPLE 57

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylacetamide

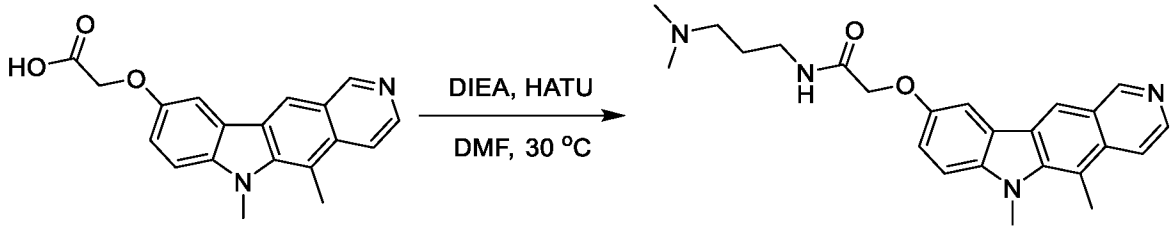


[00202] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 eq) in DMF (2 mL) was added 2-chloro-N,N-dimethylacetamide (27.8 mg, 228.7 umol, 23.5 uL, 1.2 eq), $LiOH.H_2O$ (32.0 mg, 762.4 umol, 4 eq) and NaI (28.5 mg, 190.6 umol, 1 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed some desired product was formed. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-35%, 8 min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylacet amide.

MS (ESI): m/z = 348.1 $[M+H]^+$

EXAMPLE 58

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(3(dimethylamino)propyl)-acetamide



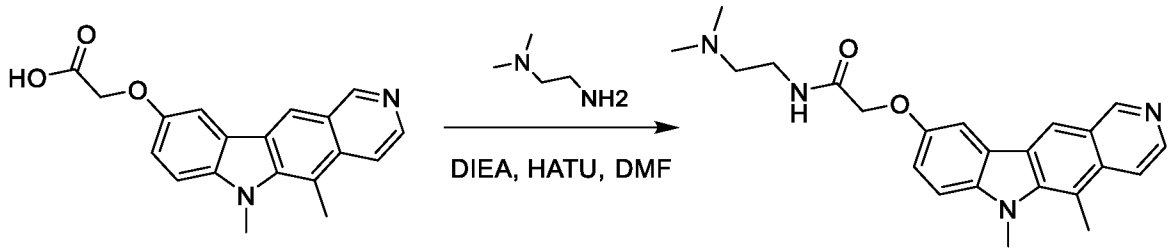
[00203] To a solution of 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetic acid (30 mg, 84.0 umol, 1 eq, HCl) in DMF (3 mL) was added DIEA (27.1 mg, 210.2 umol, 36.6

uL, 2.5 eq) and HATU (47.9 mg, 126.1 umol, 1.5 eq) and N,N-dimethylpropane-1,3-diamine (9.4 mg, 92.4 umol, 11.5 uL, 1.1 eq). The mixture was stirred at 30°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give crude product. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX C18 75*30mm*3um; mobile phase: [water(0.1%TFA)-ACN]; B%: 5%-40%, 8 min) to give 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(3-(dimethylamino)propyl)acetamide.

MS (ESI): m/z = 405.1 $[M+H]^+$

EXAMPLE 59

2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-(dimethylamino)ethyl)-acetamide

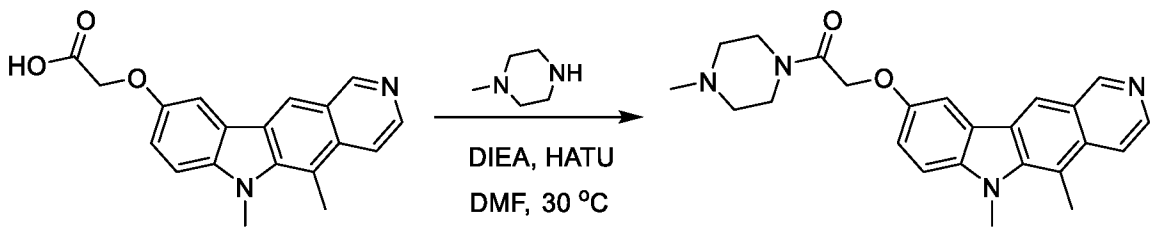


[00204] To a solution of 2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxyacetic acid (30 mg, 84.0 umol, 1 eq, HCl) in DMF (2 mL) were added N,N-dimethylethane-1,2-diamine (8.1 mg, 92.4 umol, 10.1 uL, 1.1 eq), DIEA (27.1 mg, 210.2 umol, 36.6 uL, 2.5 eq) and HATU (47.9 mg, 126.12 umol, 1.5 eq). The mixture was stirred at 30°C for 12 hr. LCMS showed the reaction was completely. The reaction mixture was concentrated under reduced pressure to remove solvent to give the residue. The residue was purified by prep-HPLC (**TFA condition**, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-40%,8min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-(dimethylamino)ethyl)acetamide.

MS (ESI): m/z = 391.1 $[M+H]^+$

EXAMPLE 60

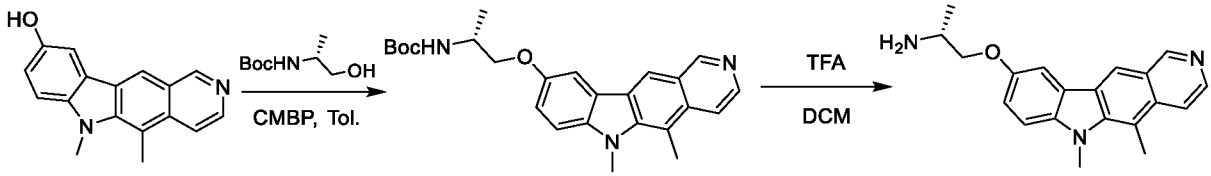
2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-1-(4-methylpiperazin-1-yl)ethanone



[00205] To a solution of 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetic acid (28 mg, 78.4 umol, 1 eq, HCl) in DMF (2 mL) was added DIEA (25.3 mg, 196.1 umol, 34.1 uL, 2.5 eq), HATU (44.7 mg, 117.7 umol, 1.5 eq) and 1-methylpiperazine (8.6 mg, 86.3 umol, 9.5 uL, 1.1 eq). The mixture was stirred at 30°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,8min) to afford 2-((5,6-dimethyl-6H-pyrido[4,3-b] carbazol-9-yl)oxy)-1-(4-methylpiperazin-1-yl)ethanone.

MS (ESI): m/z = 403.1 $[M+H]^+$

EXAMPLE 61



1 2

(R)-tert-butyl (1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)carbamate (**2**)

[00206] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (60 mg, 228.7 umol, 1 *eq*) in toluene (4 mL) was added tert-butyl N-[(1R)-2-hydroxy-1-methyl-ethyl]carbamate (40.0 mg, 228.7 umol, 1 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (110.4 mg, 457.4 umol, 2 *eq*). The mixture was stirred at 100°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=0/1) to give 80 mg of (R)-tert-butyl(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)carbamate **2**.

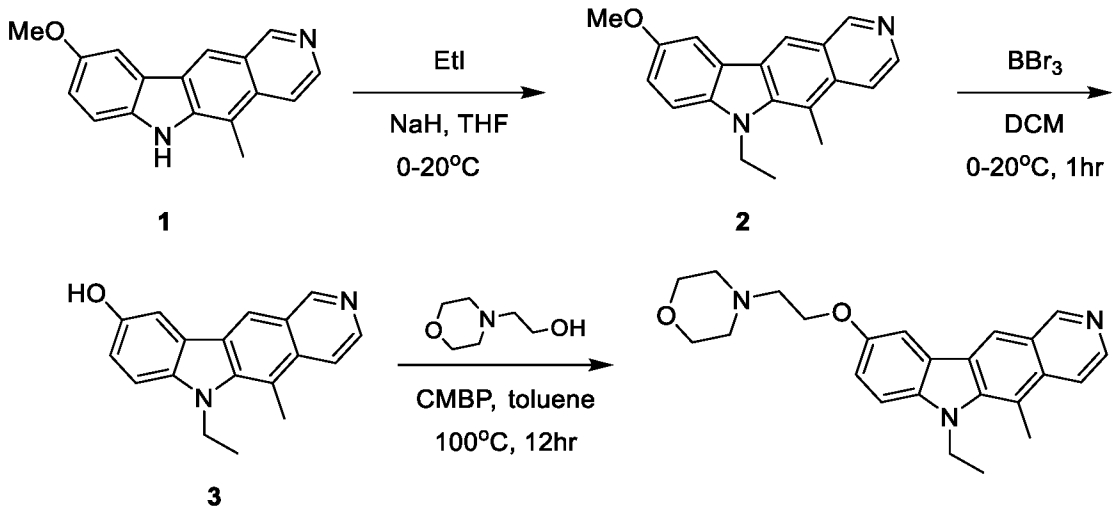
(R)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine

[00207] To a solution of (R)-tert-butyl (1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)carbamate (80 mg, 190.7 umol, 1 *eq*) in DCM (3 mL) was added TFA (3 mL). The mixture was stirred at 25°C for 2 hr. LC-MS showed **the** desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (**TFA condition**column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN]; B%: 20%-50%, 9 min) to give (R)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine.

MS (ESI): m/z = 320.1 $[M+H]^+$

EXAMPLE 62

4-[2-(6-ethyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine



Step 1: 6-ethyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00208] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (0.3 g, 1.1 mmol, 1 eq) in THF (5 mL) was added NaH (91.4 mg, 2.29mmol, 60% purity, 2 eq) at 0°C, the mixture was stirred at 0°C for 10 min, then iodoethane (214.0 mg, 1.3 mmol, 109.7 uL, 1.2 eq) was added. The mixture was stirred at 20°C for 12 hrs. LC-MS showed 9-methoxy-5- methyl-6H-pyrido[4,3-b]carbazole was consumed and desired mass was detected. The reaction mixture was quenched by addition NH_4Cl (10 mL), then diluted with water (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (15 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-ethyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole.

Step 2: 6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

[00209] To a solution of 6-ethyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole (0.2 g, 861.0 umol, 1 eq) in DCM (5 mL) was added BBr_3 (1.0 g, 4.3 mmol, 414.8 uL, 5 eq) at 0°C. The mixture was stirred at 20°C for 1 hr. LC-MS showed 6-ethyl-9-methoxy-5-methyl-pyrido [4,3-b]carbazole was consumed and desired mass was detected. The reaction mixture was quenched by addition $NaHCO_3$ 10 mL, and pressure to give a residue. 100 mL (EtOAc :MeOH = 10:1) was added, then filtered and concentrated under reduced pressure to give 6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol.

Step 3: 4-(2-((6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine

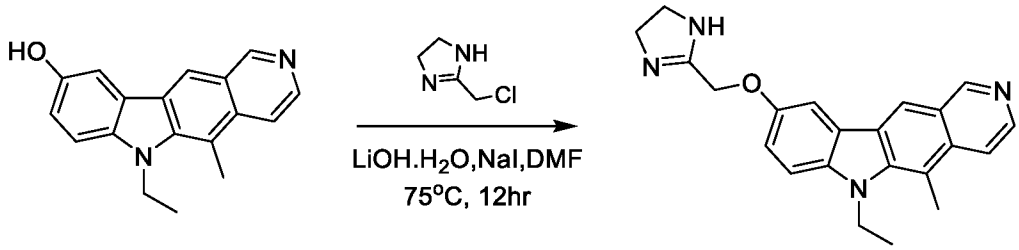
[00210] To a solution of 6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol (20 mg, 72.3 umol, 1 eq), 2-morpholinoethanol (11.3 mg, 86.8 umol, 10.6 uL, 1.2 eq) in toluene (4 mL) was added 2-(tributyl-λ5-phosphanylidene)acetonitrile (52.4 mg, 217.1 umol, 3 eq). The

mixture was stirred at 100°C for 12 hrs under N_2. LC-MS showed 6-ethyl-5-methyl-6H-pyrido [4,3-b]carbazol-9-ol was consumed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 35%-65%,10min) to give 4-[2-(6-ethyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine.

MS (ESI): m/z = 390.1 $[M+H]^+$

EXAMPLE 63

9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazole

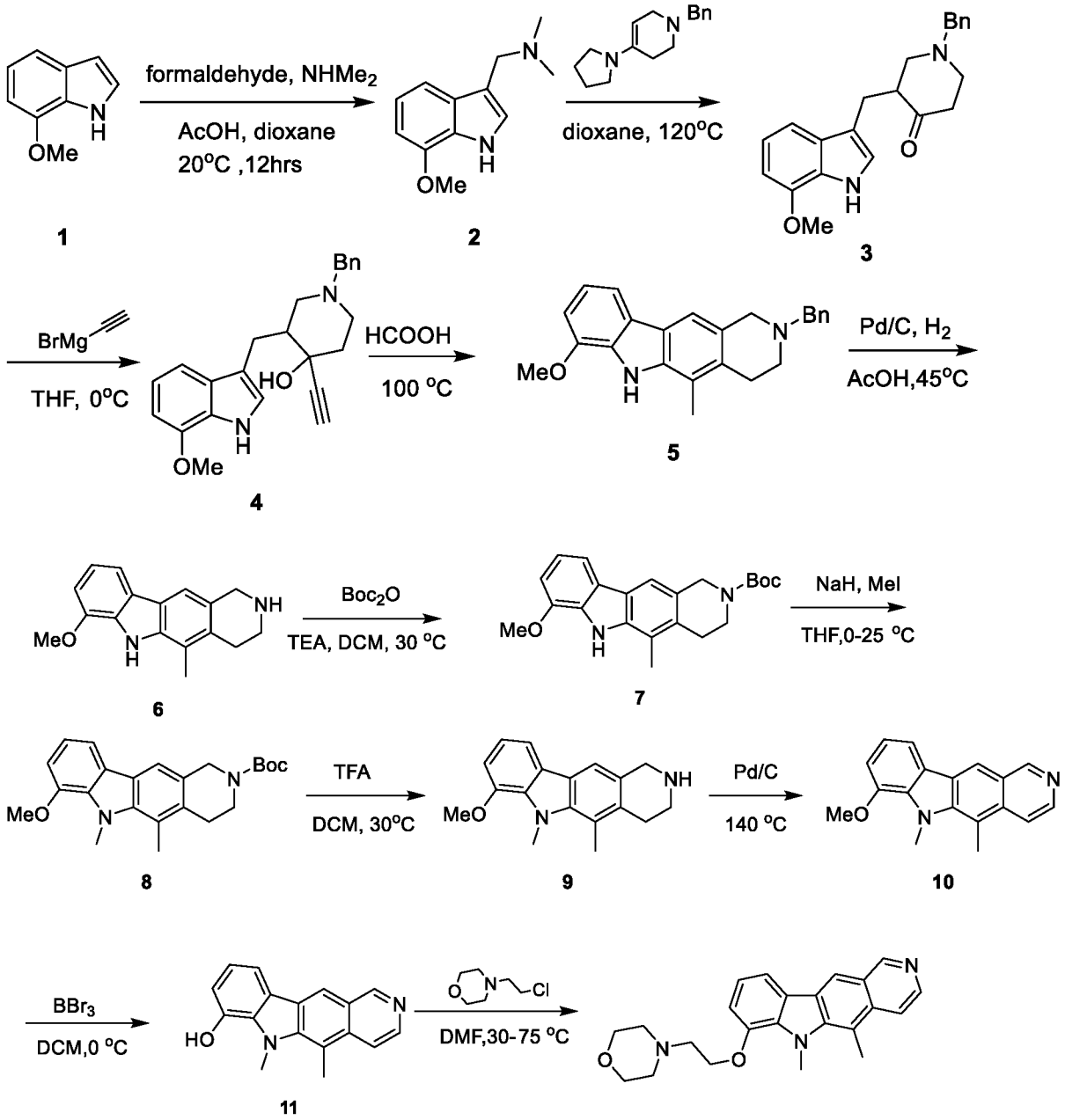


[00211] To a solution of 2-(chloromethyl)-1H-imidazole;hydrochloride (27.6 mg, 180.9 umol, 1 eq) in DMF (3 mL) was added $LiOH.H_2O$ (30.3 mg, 723.7 umol, 4 eq) and 6-ethyl-5-methyl-pyrido[4,3-b]carbazol-9-ol (50 mg, 180.9 umol, 1 eq), NaI (27.1 mg, 180.94 umol, 1 eq). The mixture was stirred at 75°C for 12 hrs. LC-MS showed 6-ethyl-5-methyl-pyrido[4,3-b]carbazol-9-ol was consumed and desired mass was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 5%-30%,8min) to give 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-ethyl-5-methyl-6H-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 359.1 $[M+H]^+$

EXAMPLE 64

4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-yl)oxy)ethyl) morpholine



Step 1: 1-(7-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[00212] To a solution of 7-methoxy-1H-indole (24 g, 163.0 mmol, 21.2 mL, 1 eq) in H_2O (100 mL) and dioxane (100 mL) was added TEA (18.1 g, 179.3 mmol, 24.9 mL, 1.1 eq), AcOH (14.69 g, 244.6 mmol, 13.9 mL, 1.5 eq), formaldehyde (14.5 g, 179.3 mmol, 13.3 mL, 37% purity, 1.1 eq) and N-methylmethanamine (25.2 g, 123.9 mmol, 28.3 mL, HCl). The mixture was stirred at 20°C for 12 hrs. LC-MS showed the desired compound was detected. The reaction was quenched by adding to saturated aqueous NaOH (2M) (150 mL), filtrated and the cake was washed with H_2O (50 mL × 3). The cake was dried under reduced pressure to give 1-(7-methoxy-1H-indol-3-yl)-N,N-dimethyl-methanamine.

Step 2: 1-benzyl-3-((7-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[00213] To a solution of 1-(7-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine (12 g, 58.7 mmol, 1 eq) in dioxane (300 mL) was added 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine (35.5 g, 146.8 mmol, 2.5 eq). The mixture was stirred at 120°C for 12 hrs. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between H_2O (80mL) and EtOAc (80mL). The aqueous phase was washed with EtOAc (60 mL × 3). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 50 mL/min) to give 1-benzyl-3-((7-methoxy-1H-indol-3-yl)methyl) piperidin-4-one.

Step 3: 1-benzyl-4-ethynyl-3-((7-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[00214] To a solution of 1-benzyl-3-((7-methoxy-1H-indol-3-yl)methyl)piperidin-4-one (20 g, 57.4 mmol, 1 eq) in THF (200 mL) was added bromo(ethynyl)magnesium (0.5 M, 344.3 mL, 3 eq). The mixture was stirred at 0°C for 2 hrs. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl (80 mL) and EtOAc (80 mL). The aqueous phase was washed with EtOAc (80 mL × 2). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-benzyl-4-ethynyl-3-((7-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol.

Step 4: 2-benzyl-7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00215] The solution of 1-benzyl-4-ethynyl-3-((7-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol (18 g, 48.0 mmol, 1 eq) in HCOOH (200 mL) was stirred at 100°C for 12 hrs. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was partitioned between $NaHCO_3$ (60 mL) and EtOAc (60 mL). The aqueous phase was washed with EtOAc (50 mL × 2). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give 2-benzyl-7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 5: 7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00216] A mixture of 2-benzyl-7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (5 g, 14.0 mmol, 1 eq), Pd/C (2 g, 10% purity, 1 eq) in AcOH (20 mL) was degassed and purged with H_2 (15 Psi) for 3 times, and then the mixture was stirred at 45°C for 2 hrs under H_2 (15 Psi) atmosphere. LC-MS showed the desired compound was

detected. The reaction mixture was filtered and concentrated under reduced pressure to give 7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 6: tert-butyl 7-methoxy-5-methyl-3,4-dihydro-1H-pyrido[4,3-b]carbazole-2(6H)-carboxylate

[00217] To a solution of 7-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (850 mg, 3.1 mmol, 1 eq) in DCM (5 mL) was added Boc_2O (1.3 g, 6.3 mmol, 1.47 mL, 2 eq) and TEA (968.8 mg, 9.5 mmol, 1.3 mL, 3 eq). The mixture was stirred at 30°C for 3 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether / Ethyl acetate = 3/1) to give tert-butyl 7-methoxy-5-methyl-3,4-dihydro-1H- pyrido[4,3-b]carbazole-2(6H)-carboxylate.

Step 7: tert-butyl7-methoxy-5,6-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]carbazole-2(6H)-carboxylate

[00218] To a solution of tert-butyl 7-methoxy-5-methyl-1,3,4,6-tetrahydropyrido[4,3-b]carbazole -2-carboxylate (530 mg, 1.4 mmol, 1 eq) in THF (8 mL) was added NaH (115.7 mg, 2.8 mmol, 60% purity, 2 eq) at 0°C and stirred for 10 min, MeI (184.7 mg, 1.3 mmol, 81.0 uL, 0.9 eq) was added to the mixture at 0°C. The mixture was stirred at 25°C for 12 hrs. LC-MS showed most desired compound was detected. The reaction mixture was quenched by addition NH_4Cl (10 mL) and extracted with Ethyl acetate (6 mL × 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 = 1/1) to give tert-butyl 7-methoxy-5,6-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]carbazole-2(6H)-carboxylate.

Step 8: 7-methoxy-5,6-dimethyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00219] To a solution of tert-butyl 7-methoxy-5,6-dimethyl-3,4-dihydro-1H-pyrido[4,3-b]carbazole -2(6H)-carboxylate (310 mg, 814.7 umol, 1 eq) in DCM (4 mL) was added TFA (1.8 g, 16.3 mmol, 1.2 mL, 20 eq). The mixture was stirred at 30°C for 1 hr. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The reaction mixture was added MeOH (15 mL), pH was adjusted to around 7-8 by progressively adding TEA, then the reaction mixture was concentrated under reduced pressure to give 7-methoxy-5,6-dimethyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

Step 9: 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00220] To a solution of Pd/C (100 mg, 10% purity, 1 eq) in xylene (8 mL) was added 7-methoxy-5,6-dimethyl-1,2,3,4-tetrahydropyrido[4,3-b]carbazole (220 mg, 784.7 umol, 1 eq). The mixture was stirred at 140°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

Step 10: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol

[00221] To a solution of 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (38 mg, 137.5 umol, 1 eq) in DCM (2 mL) was added BBr_3 (206.7 mg, 825.0 umol, 79.5 uL, 6 eq) at 0°C. The mixture was stirred at 0°C for 2 hrs. LC-MS showed most desired compound was detected. The reaction mixture was diluted with $NaHCO_3$ (15 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over (Na_2SO_4), filtered and concentrated under reduced pressure to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol.

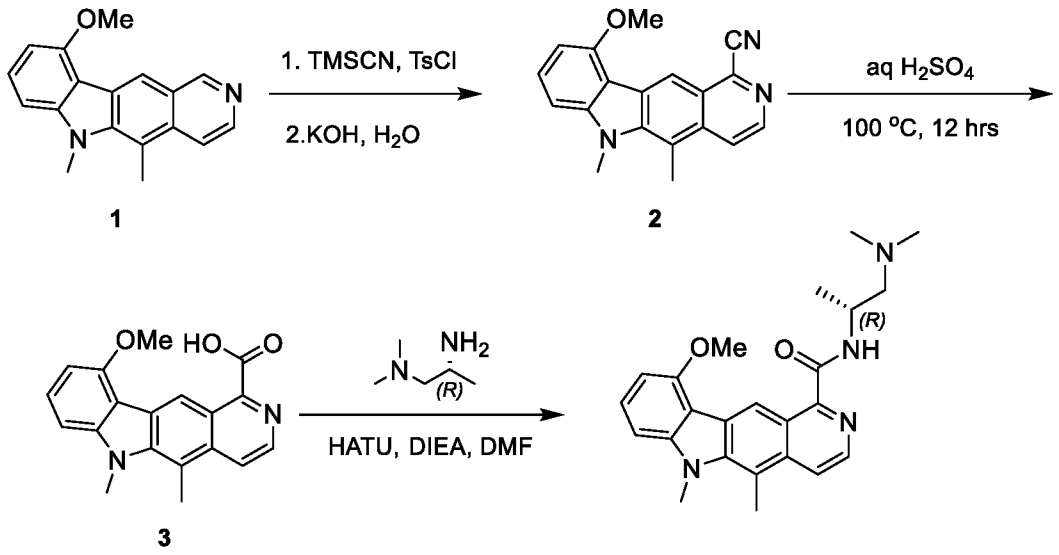
Step 11: 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-yl)oxy)ethyl)morpholine

[00222] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol (50 mg, 190.6 umol, 1 eq) in DMF (4 mL) was added NaI (5.71 mg, 38.1 umol, 0.2 eq) and 4-(2-chloroethyl)morpholine;hydrochloride (35.47 mg, 190.6 umol, 1 eq), $LiOH.H_2O$ (39.9 mg, 953.0 umol, 5 eq) at 30°C. The mixture was stirred at 75°C for 2 hrs. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 2%-25%,8min) to give 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-yl)oxy)ethyl) morpholine.

MS (ESI): m/z = 376.1 $[M+H]^+$

EXAMPLE 65

(R)-N-(1-(dimethylamino)propan-2-yl)-10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide



Step 1: 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00223] To a solution of 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (550 mg, 1.9 mmol, 1 eq) in DCM (5 mL) was added TMSCN (513.3 mg, 5.1 mmol, 647.4 uL, 2.6 eq). A solution of TosCl (720.9 mg, 3.7 mmol, 1.9 eq) in DCM (5 mL) was dropwsie added to the above mixture at 25°C. The mixture was stirred at 25°C for 12 hr. LCMS showed the intermediate was detected and 5 mL KOH (50% W/W) was added. The mixture was stirred at 25°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between H_2O 50 mL and CH_2Cl_2 50 mL. The aqueous phase was separated, washed with CH_2Cl_2 (50 mL × 3), the organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

Step 2: 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

[00224] To a solution of 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (100 mg, 331.8 umol, 1 eq) in H_2SO_4 (2 mL, 98% purity) and H_2O (2 mL) was stirred at 110°C for 12 hr. LC-MS showed the desired compound was detected. The mixture was poured into $NaHCO_3$ (200 mL) and the brown solid was separate out. Then the mixture was filtered and collect the solid to afford 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

Step 3: (R)-N-(1-(dimethylamino)propan-2-yl)-10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

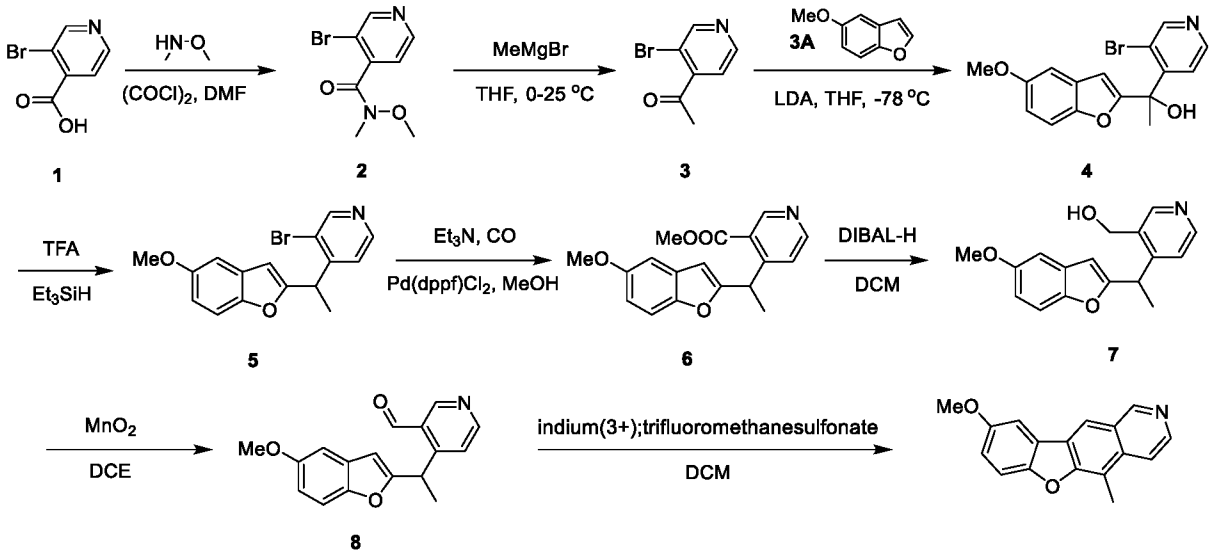
[00225] To a solution of 10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (100 mg, 312.1 umol, 1 eq) in DMF (2 mL) was added (2R)-N1,N1-dimethylpropane-1,2-diamine (163.9 mg, 936.5 umol, 3 eq, 2HCl), DIEA (201.7 mg, 1.5

mmol, 271.8 uL, 5 eq) and HATU (237.3 mg, 624.3 umol, 2 eq) at 0°C. The mixture was stirred at 25°C for 1 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give crude product. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-40%, 8 min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

MS (ESI): m/z = 405.1 $[M+H]^+$

EXAMPLE 66

9-methoxy-5-methyl-benzofuro[2,3-g]isoquinoline



Step 1: 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide

[00226] To a solution of 3-bromopyridine-4-carboxylic acid (5 g, 24.7 mmol, 1 eq) and DMF (1.8 g, 24.7 mmol, 1.9 mL, 1 eq) in DCM (100 mL) was added $(COCl)_2$ (3.8 g, 29.7 mmol, 2.6 mL, 1.2 eq) and then the reaction mixture was stirred at 15 °C for 1 hr. Then the mixture was concentrated to give residue. The residue was dissolved in DCM (100 mL) and Py (4.3 g, 54.4 mmol, 4.4 mL, 2.2 eq), N-methoxymethanamine (2.66 g, 27.23 mmol, 1.1 eq, HCl) was added. The reaction mixture was stirred at 15°C for 12 hr. TLC (Petroleum ether/Ethyl acetate = 1/1, Rf = 0.30) indicated 3-bromopyridine-4-carboxylic acid was consumed completely and one new spot formed. The reaction mixture was added to saturated $NaHCO_3$ (100 mL) and extracted with ethyl acetate (100 mL × 3). The combined organic phase was washed with brine (100 mL × 1), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g Sepa Flash® Silica Flash Column, Eluent of 0~30% Ethyl acetate / Petroleum

ether gradient @ 100 mL/min) (Petroleum ether/Ethyl acetate = 1/1, Rf = 0.30) to give 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide.

Step 2: 1-(3-bromo-4-pyridyl)ethanone

[00227] To a solution of 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide (2.5 g, 10.2 mmol, 1 eq) in THF (25 mL) was added bromo(methyl)magnesium (3 M, 6.8 mL, 2 eq) at 0°C and then the reaction mixture was stirred at 20°C for 12 hr. TLC (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.70) indicated 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide was consumed and one new spot formed. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g Sepa Flash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.70) to give purified 1-(3-bromo-4-pyridyl)ethanone.

Step 3: 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzofuran-2-yl)ethanol

[00228] To a stirred solution of 5-methoxybenzofuran (814.7 mg, 5.5 mmol, 1.1 eq) in THF(10 mL) was added LDA (2 M, 3.0 mL, 1.2 eq) at -78°C under N_2 for 0.5 hr. Then a solution of 1-(3-bromo-4-pyridyl)ethanone (1 g, 5.00 mmol, 1 eq) in THF(10 mL) was added and stirred at -78°C under N_2 for 1 hr. TLC (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.60) indicated 1-(3-bromo-4-pyridyl)ethanone was remained and one new spot formed. The reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 28~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) TLC (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.60） to give 1 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzofuran-2-yl)ethanol.

Step 4: 3-bromo-4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine

[00229] To a solution of 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzofuran-2-yl)ethanol (500 mg, 1.44 mmol, 1 eq) in TFA (8 mL) was added Et_3SiH (333.9 mg, 2.9 mmol, 458.7 uL, 2 eq) at 20°C and then the reaction mixture was stirred at 30°C for 12 hr. LCMS showed 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzofuran-2-yl)ethanol was consumed and 46% of desired compound was detected. The reaction mixture was concentrated and then adjusted to pH=8 by saturated $NaHCO_3$ solution. The aqueous phase was extracted with dichloromethane (20 mL × 4). The combined organic phase was dried over anhydrous Na_2SO_4, filltered and concentrated in vacuum. The residue was purified by flash silica gel

chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) TLC (Petroleum ether/Ethyl acetate = 0/1, Rf = 0.70) to give purified 3-bromo-4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine.

Step 5: methyl 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carboxylate

[00230] To a solution of 3-bromo-4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine (500 mg, 1.51 mmol, 1 eq) in MeOH (15 mL) was added Et_3N (456.92 mg, 4.52 mmol, 628.50 uL, 3 eq) and $Pd(dppf)Cl_2$ (220.27 mg, 301.03 umol, 0.2 eq) under N_2 at 20 °C. Then the reaction mixture was stirred at 80 °C under CO (50 psi) for 12 hr. LCMS showed 3-bromo-4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine was consumed and 60% of desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 4 g Sepa Flash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) TLC (Petroleum ether/Ethyl acetate= 0/1, Rf = 0.60) to give purified methyl 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carboxylate.

Step 6: [4-[1-(5-methoxybenzofuran-2-yl)ethyl]-3-pyridyl]methanol

[00231] To a solution of methyl 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carboxylate (75 mg, 240.9 umol, 1 eq) in DCM (2 mL) was added DIBAL-H (1 M, 722.7 uL, 3 eq) slowly at -78°C under N_2 for 4 hr. LCMS showed 49% of methyl 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carboxylate was remained and 30% of desired compound was detected. The reaction mixture was quenched with saturated aqueous potassium sodium tartrate (8 mL) and extracted with dichloromethane (8 mL × 3). The combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO2, Ethyl acetate/Ethanol = 3/1) TLC (Ethyl acetate/Ethanol = 3/1, Rf = 0.35) to give purified [4-[1-(5-methoxybenzofuran-2-yl)ethyl]-3-pyridyl]methanol.

Step 7: 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carbaldehyde

[00232] To a solution of [4-[1-(5-methoxybenzofuran-2-yl)ethyl]-3-pyridyl]methanol (26 mg, 91.77 umol, 1 eq) in DCE (2 mL) was added MnO_2 (159.56 mg, 1.84 mmol, 20 eq) at 20°C and then the reaction mixture was stirred at 20°C for 12 hr. LCMS showed 5% of Reactant 1 was remained and 73% of desired compound was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate = 0/1) TLC (Petroleum ether/Ethyl acetate = 0/1 Rf = 0.60) to give purified 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carbaldehyde.

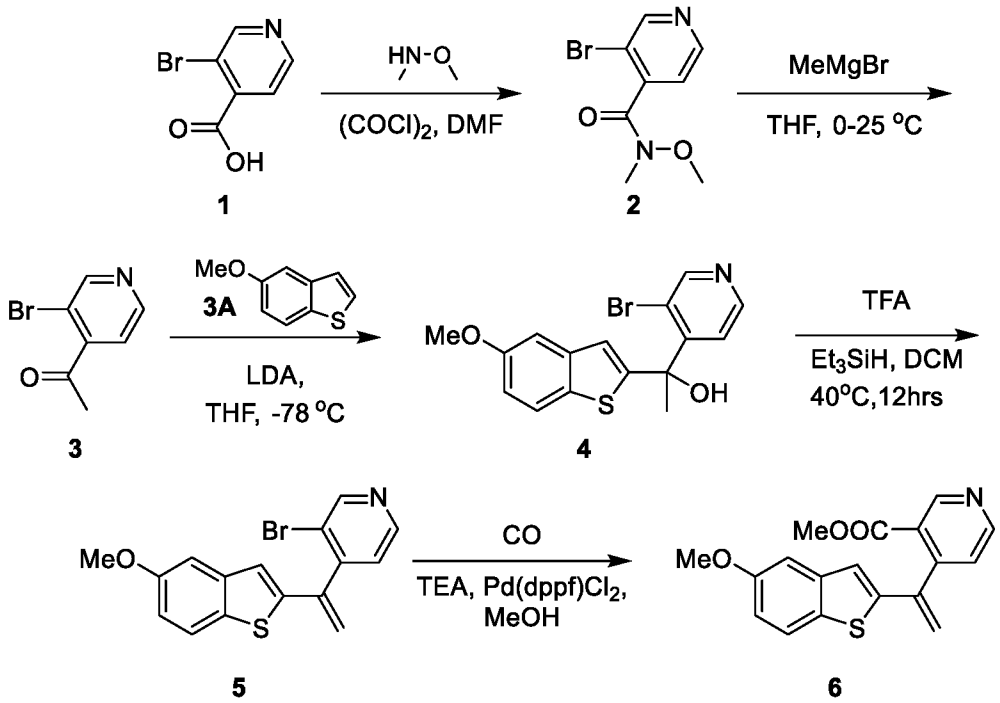
Step 8: 9-methoxy-5-methyl-benzofuro[2,3-g]isoquinoline

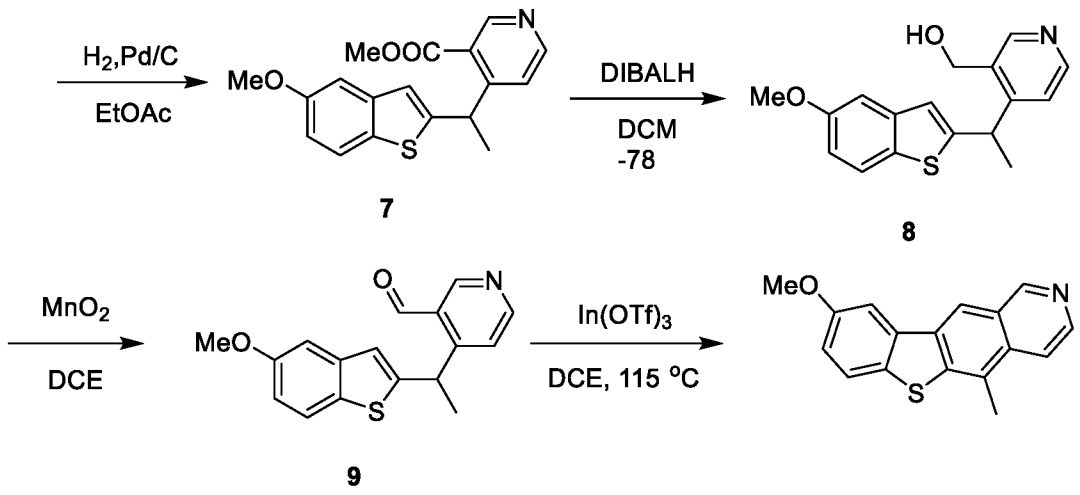
[00233] To a solution of 4-[1-(5-methoxybenzofuran-2-yl)ethyl]pyridine-3-carbaldehyde (15 mg, 53.3 umol, 1 eq) in DCE (2 mL) was added indium(3+);trifluoromethanesulfonate (3.00 mg, 5.3 umol, 0.1 eq) and then the reaction mixture was stirred at 115°C for 12 hr. LCMS showed 4% of Reactant 1 was remained and 78% of desired compound was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 40%-75%,8min) to give purified 9-methoxy-5-methyl-benzofuro[2,3-g]isoquinoline.

MS (ESI): m/z = 264.0 $[M+H]^+$

EXAMPLE 67

9-methoxy-5-methyl-benzothiopheno[2,3-g]isoquinoline





Step 1: 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide

[00234] To a solution of 3-bromopyridine-4-carboxylic acid (2 g, 9.9 mmol, 1 eq) in 20 mL of DCM and DMF (72.4 mg, 990.1 μmol, 0.1 eq) was added $(COCl)_2$ (1.5 g, 11.9 mmol, 1.0 mL, 1.2 eq) at 20°C. The mixture was stirred at 20°C for 1 hr to give a colorless solution, which was cooled to 0°C, N-methoxymethanamine hydrochloride (1.5 g, 14.9 mmol, 1.5 eq) and Py (1.7 g, 21.8 mmol, 1.8 mL, 2.2 eq) were added and the mixture was stirred at 20°C for 12 hrs. LCMS showed the reaction was complete and desired product was detected. The reaction mixture was quenched by addition of 30 mL of sat. $NaHCO_3$, and then extracted three times with 300 mL of ethyl acetate. The combined organic layers were washed with 100 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether/ethyl acetate=1/0 to 0/1) to give crude 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide.

Step 2: 1-(3-bromo-4-pyridyl)ethanone

[00235] To a solution of 3-bromo-N-methoxy-N-methyl-pyridine-4-carboxamide (1.9 g, 7.8 mmol, 1 eq) in 20 mL of THF was added MeMgBr (3M, 7.8 mL, 3 eq) at 0°C. The mixture was stirred at 0°C for 2 hrs. LCMS showed the reaction was complete and desired product was detected. The reaction mixture was quenched by addition of 50 mL sat. NH_4Cl, extracted three times with 60 mL of ethyl acetate. The combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether/ethyl acetate=100/1 to 20/1) to give crude 1-(3-bromo-4-pyridyl)ethanone.

Step 3: 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzothiophen-2-yl) ethanol

[00236] To a solution of 5-methoxybenzothiophene (0.7 g, 4.3 mmol, 1 eq) in 15 mL of THF was added dropwise LDA (2M, 2.6 mL, 1.2 eq) at -78°C. After addition, the mixture was stirred at this temperature for 0.5 hr, and then 1-(3-bromo-4-pyridyl)ethanone (852.6 mg, 4.3 mmol, 1 eq) in 5 mL of THF was added dropwise at -78°C. The resulting mixture was stirred at -78°C for 0.5 hr. TLC showed the reaction was complete. The reaction mixture was quenched by addition of 100 mL of sat. NH_4Cl, and then diluted with 50 mL of water and extracted twice with 200 mL of ethyl acetate. The combined organic layers were washed with 100 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether/ethyl acetate=1/1 to 0/1) to give crude 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzothiophen-2-yl) ethanol.

Step 4: 3-bromo-4-[1-(5-methoxybenzothiophen-2-yl)vinyl]pyridine

[00237] A mixture of 1-(3-bromo-4-pyridyl)-1-(5-methoxybenzothiophen-2-yl)ethanol (1.25 g, 3.4 mmol, 1 eq) in 5 mL of DCM was cooled to 0°C, triethylsilane (1.0 g, 8.9 mmol, 1.4 mL, 2.6 eq) and TFA (6.5 g, 56.8 mmol, 4.2 mL, 16.6 eq) were added, then the mixture was stirred at 45°C for 12 hrs. TLC showed the reaction was complete. The reaction mixture was quenched by addition of 50 mL of sat. $NaHCO_3$ at 0°C, and then diluted with 20 mL of H_2O and extracted twice with 200 mL of ethyl acetate. The combined organic layers were washed with 50 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether/ethyl acetate=1/0 to 4/1) to give crude 3-bromo-4-[1-(5-methoxybenzothiophen-2-yl)vinyl]pyridine.

Step 5: 4-[1-(5-methoxybenzothiophen-2-yl)vinyl]pyridine-3-carboxylate

[00238] A mixture of 3-bromo-4-[1-(5-methoxybenzothiophen-2-yl)vinyl]pyridine (0.1 g, 288.8 µmol, 1 eq), TEA (146.1 mg, 1.4 mmol, 201.0 µL, 5 eq), $Pd(dppf)Cl_2$ (21.1 mg, 28.9 µmol, 0.1 eq) in 10 mL of MeOH was degassed and purged with CO for 3 times, and then the mixture was stirred at 75°C for 12 hrs under CO atmosphere (50 Psi). LCMS showed the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, eluting with petroleum ether: ethyl acetate = 1:1) to give Methyl4-[1-(5-methoxy benzothiophen-2-yl)vinyl]pyridine-3-carboxylate.

Step 6: methyl 4-[1-(5-methoxybenzothiophen-2-yl)ethyl]pyridine-3-carboxylate

[00239] A mixture of methyl 4-[1-(5-methoxybenzothiophen-2-yl)vinyl]pyridine-3-carboxylate (50 mg, 153.7 µmol, 1 eq), Pd/C (30 mg, 10% purity) in 10 mL of ethyl acetate was degassed and purged with H_2 for 3 times, and then the mixture was stirred at 20°C for

0.5 hr under H_2 atmosphere (15 Psi). LCMS showed the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure to give crude methyl 4-[1-(5-methoxybenzothiophen-2-yl)ethyl]pyridine-3-carboxylate.

Step 7: [4-[1-(5-methoxybenzothiophen-2-yl)ethyl]-3-pyridyl]methanol

[00240] A mixture of methyl 4-[1-(5-methoxybenzothiophen-2-yl)ethyl]pyridine-3-carboxylate (100 mg, 305.4 μmol, 1 eq) in 2 mL of DCM was degassed and purged with N_2 for 3 times, then DIBAL-H (1M, 916.32 μL, 3 eq) was added at -78°C, and then the mixture was stirred at -78°C for 4 hrs under N_2 atmosphere. LCMS showed the reaction was complete. The mixture was cooled to 0°C, 0.04 mL of H_2O and 0.04 mL of 15% NaOH solution was added, followed by addition of 0.1 mL of H_2O, the mixture was stirred at 20°C for 10 min, filtered and concentrated under reduced pressure to give crude [4-[1-(5-methoxybenzothiophen-2-yl)ethyl]-3-pyridyl]methanol.

Step 8: 4-[1-(5-methoxybenzothiophen-2-yl)ethyl]pyridine-3-carbaldehyde

[00241] A mixture of [4-[1-(5-methoxybenzothiophen-2-yl)ethyl]-3-pyridyl]methanol (40 mg, 133.6 μmol, 1 eq), MnO_2 (58.1 mg, 668.0 μmol, 5 eq) in 1 mL of DCE was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 40°C for 12 hrs. LCMS showed the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure to give crude 4-[1-(5-methoxybenzothiophen-2-yl) ethyl]pyridine-3-carbaldehyde.

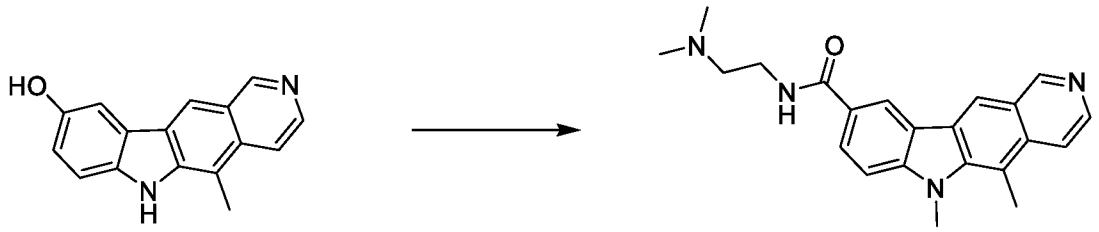
Step 9: 9-methoxy-5-methyl-benzothiopheno[2,3-g]isoquinoline

[00242] A mixture of 4-[1-(5-methoxybenzothiophen-2-yl)ethyl]pyridine-3-carbaldehyde (40 mg, 134.5 μmol, 1 eq), indium(3+) trifluoromethanesulfonate (3.8 mg, 6.7 μmol, 0.05 eq) in 2 mL of DCE was stirred at 115°C for 12 hrs. LCMS showed the reaction was complete. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (FA condition, column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 30%-50%,10min) to give 9-methoxy-5-methyl-benzothiopheno[2,3-g]isoquinoline.

MS (ESI): m/z = 280.00 $[M+H]^+$

EXAMPLE 68

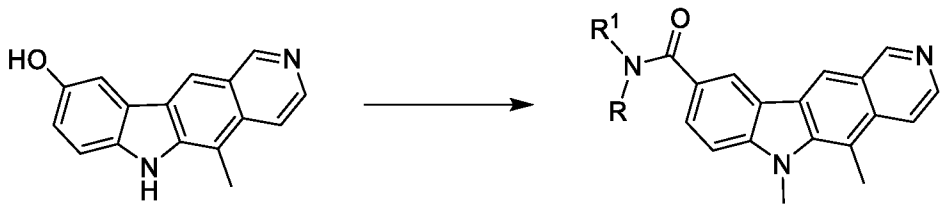
N-(2-(dimethylamino)ethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide



[00243] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (52 mg, 0.20 mmol) in DCM (1 ml) and pyridine (25 uL, 0.30 mmol) was added trifluoromethanesulfonic anhydride (56 mg, 0.2 mmol) at 0 °C and warmed up to rt, then stirred overnight at rt. To the mixture was added water and EtOAc, and the org phase was washed with NaHCO3 aq and brine, dried over Na2SO4 and concentrated. The residue was dissolved in toluene (1 ml) and Pd(dppf)Cl2 (10 mg, 0.01 mmol) and 2,4,6-trichlorophenylformate (45 mg, 0.2 mmol) were added. DBU (30 uL, 0.2 mmol) was then added and the mixture was heated at 80 °C overnight under N2, then added NH4Cl aq and DCM. The org phase was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was dissolved in THF (1 ml) and 2-(dimethylamino)-ethylamine (88 mg, 1.0 mmol) was added and the mixture stirred overnight at rt. The crude product was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the title compound.

MS (ESI): 361.2 [M+H]+

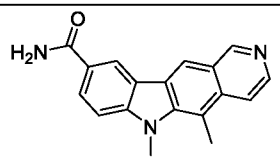
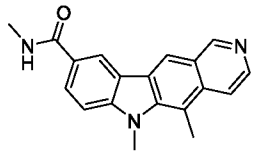
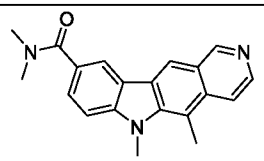
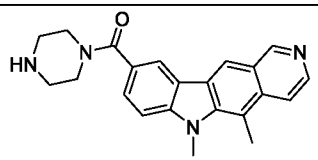
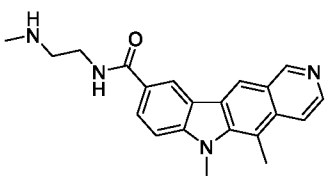
[00244] EXAMPLES 69-79

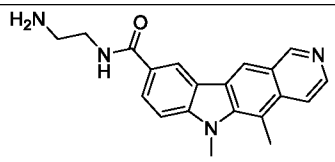
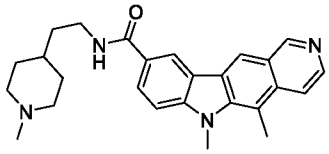
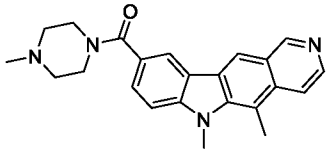
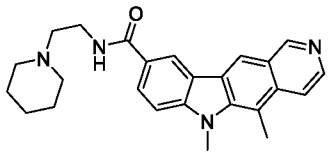
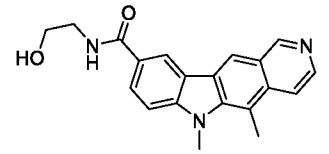
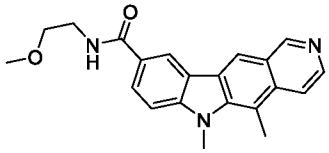


General Procedure:

[00245] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (140 mg, 0.53 mmol) in DCM (1 ml) and pyridine (100 uL, 1.20 mmol) was added trifluoromethanesulfonic anhydride (280 mg, 1.0 mmol) at 0 °C and warmed up to rt, then stirred overnight at rt. To the mixture was added water and EtOAc, and the org phase was washed with NaHCO3 aq and brine, dried over Na2SO4 and concentrated. The residue was dissolved in toluene (5

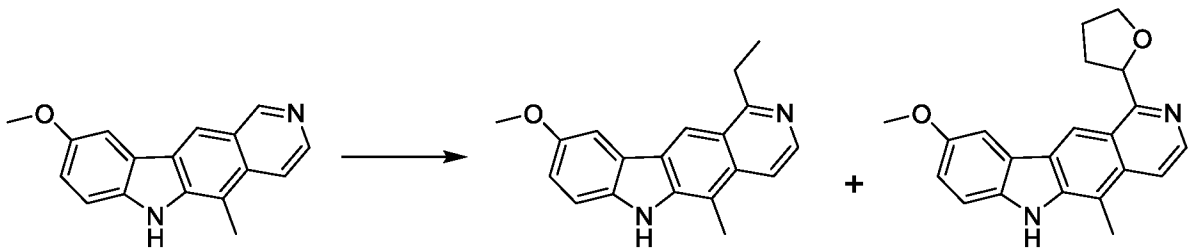
ml) and Pd(dppf)Cl2 (50 mg, 0.05 mmol) and 2,4,6-trichlorophenylformate (225 mg, 1.0 mmol) were added. DBU (150 uL, 1.0 mmol) was then added and the mixture was heated at 80 °C overnight under N2, then added NH4Cl aq and DCM. The org phase was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was dissolved in THF (1 ml) and the appropriate amine R^1RNH (0.5 mmol) was added and the mixture stirred overnight at rt. The crude product was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the product as shown in the table below.

Example #	Compound Name	MS (ESI)	Structure
69	5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	290.1 [M+H]+	
70	N,5,6-trimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	304.1 [M+H]+	
71	N,N,5,6-tetramethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	318.2 [M+H]+	
72	(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)(piperazin-1-yl)methanone	358.2 [M+H]+	
73	5,6-dimethyl-N-(2-(methylamino)ethyl)-6H-pyrido[4,3-b]carbazole-9-carboxamide	347.2 [M+H]+	

74	N-(2-aminoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	332.2 [M+H]+	
75	5,6-dimethyl-N-(2-(1-methylpiperidin-4-yl)ethyl)-6H-pyrido[4,3-b]carbazole-9-carboxamide	415.2 [M+H]+	
76	(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)(4-methylpiperazin-1-yl)methanone	373.2 [M+H]+	
77	5,6-dimethyl-N-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole-9-carboxamide	401.2 [M+H]+	
78	N-(2-hydroxyethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	334.5 [M+H]+	
79	N-(2-methoxyethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	334.1 [M+H]+	

EXAMPLE 80

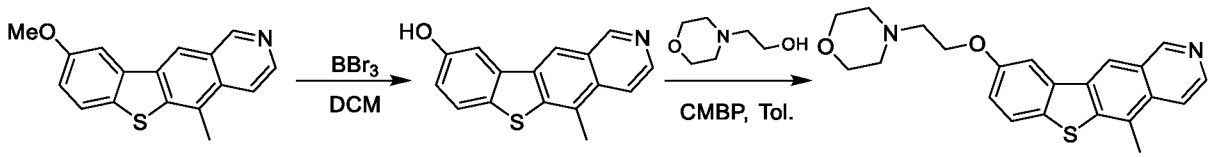
1-ethyl-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (80a) & 9-methoxy-5,6-dimethyl-1-(tetrahydrofuran-2-yl)-6H-pyrido[4,3-b]carbazole (80b)



[00246] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (14 mg, 0.05 mmol) and Ir(ppy)2(dtbpy)PF6 (1.8 mg, 0.0002 mmol) in DMSO (0.1 ml) was added methyl thioglycolate (2 uL, 0.01 mmol), pTSA (38 mg, 0.2 mmol) and EtOH or THF (50 uL). The mixture was stirred at rt in front of blue LED light overnight. The resulting mixture was purified by HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford 1-ethyl-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole and 9-methoxy-5,6-dimethyl-1-(tetrahydrofuran-2-yl)-6H-pyrido[4,3-b]carbazole.

EXAMPLE 81

4-[2-(5-methylbenzothiopheno[2,3-g]isoquinolin-9-yl)oxyethyl]morpholine



Step 1. 5-methylbenzothiopheno[2,3-g]isoquinolin-9-ol

[00247] To a solution of 9-methoxy-5-methyl-benzothiopheno[2,3-g]isoquinoline (90 mg, 322.1 µmol, 1 eq) in DCM (3 mL) was added BBr3 (161.4 mg, 644.3µmol, 2 eq) at 0°C. The mixture was stirred at 0°C for 1hr. LCMS showed the 9-methoxy-5-methyl-benzothiopheno [2,3-g]isoquinoline remained and the desired ms was detected then the mixture was stirred at 0°C for another 3hr, LCMS showed the reaction was complete. The reaction mixture was poured into 50 mL of sat.NaHCO3 at 0 °C, and then diluted with 50 mL of H2O and extracted with 300 mL of ethyl acetate. The combined organic layers were washed with 200 mL of brine, dried over Na2SO4, filtered and concentrated under reduced pressure to give 5-methylbenzothiopheno[2,3-g]isoquinolin-9-ol.

Step 2. 4-[2-(5-methylbenzothiopheno[2,3-g]isoquinolin-9-yl)oxyethyl]morpholine

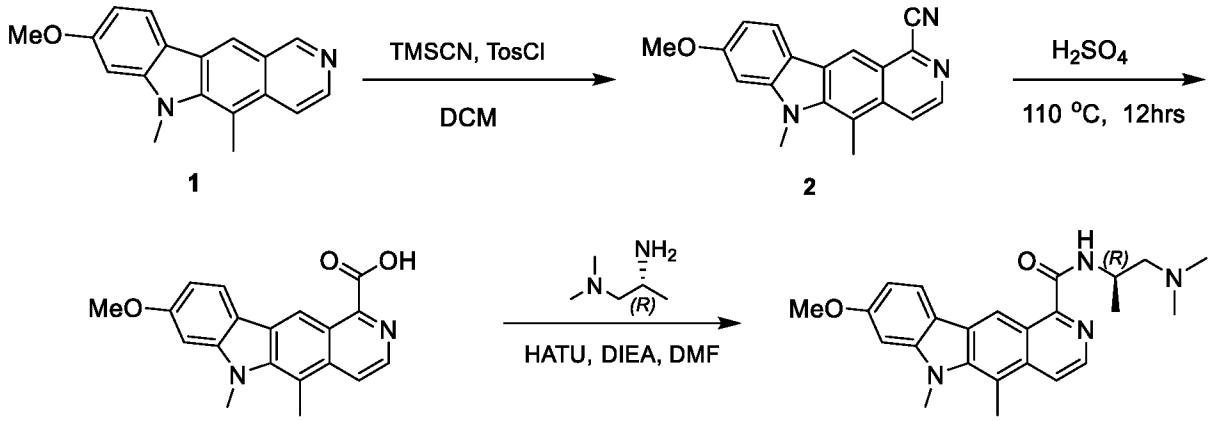
[00248] A mixture of 2-morpholinoethanol (49.44 mg, 376.89µmol, 2 eq), 5-methylbenzothiopheno [2,3-g]isoquinolin-9-ol (50 mg, 188.45µmol, 1 eq) , 2-(tributyl-λ^5-phosphanylidene) acetonitrile (68.22 mg, 282.67µmol, 1.5 eq) in toluene (2 mL), and then the mixture was stirred at 100°C for 12hr. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition, column: 3_Phenomenex Luna C18

75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 5%-40%,8min) to give 4-[2-(5-methylbenzothiopheno[2,3-g]isoquinolin-9-yl)oxyethyl]morpholine.

MS (ESI): m/z = 379.00 $[M+H]^+$

EXAMPLE 82

(R)-N-(1-(dimethylamino)propan-2-yl)-8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide



Step 1: 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00249] To a solution of 8-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole (0.6 g, 2.1 mmol, 1 eq) in DCM (20 mL) was added TMSCN (560.0 mg, 5.6 mmol, 706.2 uL, 2.6 eq). A solution of TosCl (786.5 mg, 4.1 mmol, 1.9 eq) in DCM (2 mL) was dropwsie added to the above mixture at 25°C. The mixture was stirred at 25°C for 12 hr. 10 mL KOH (50% W/W) was added to the above mixture. The mixture was stirred at 25°C for 2 hr. TLC showed the reaction was completely. The reaction was extracted with DCM (30 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

Step 2: 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

[00250] The mixture of 8-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carbonitrile (600 mg, 1.9 mmol, 1 eq) in H_2SO_4 (6 mL, 98% purity) and H_2O (6 mL) was stirred at 110°C for 12 hr. LCMS showed some desired product was formed. The reaction was poured into saturated aqueous $NaHCO_3$ (80 mL) and filtered. The cake was dried to give 8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

Step 3: (R)-N-(1-(dimethylamino)propan-2-yl)-8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

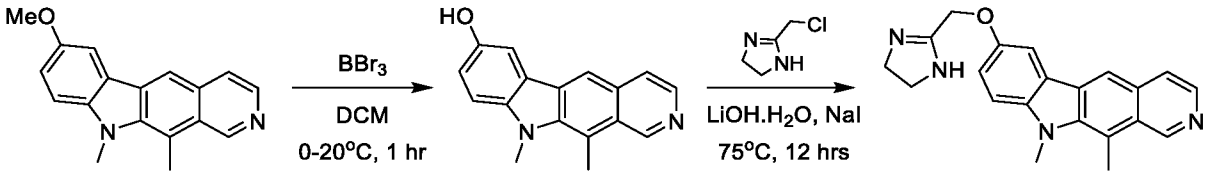
[00251] To a solution of 8-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxylic acid (600 mg, 1.8 mmol, 1 eq) in DMF (20 mL) was added DIEA (1.2 g, 9.3 mmol, 1.6 mL, 5

eq) and (2R)-N1,N1-dimethylpropane-1,2-diamine (259.6 mg, 1.8 mmol, 1 eq, HCl). The mixture was cooled to 0°C and HATU (2.1 g, 5.6 mmol, 3 eq) was added. The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Kromasil C18 (250*50mm*10 um);mobile phase: [water(10mM NH4HCO3)-ACN];B%: 35%-55%,10min) to afford (R)-N-(1-(dimethylamino)propan-2-yl)-8-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

MS (ESI): m/z = 405.2 $[M+H]^+$

EXAMPLE 83

7-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-10,11-dimethyl-pyrido[3,4-b]carbazole



Step 1. 10,11-dimethyl-10H-pyrido[3,4-b]carbazol-7-ol

[00252] To a solution of 7-methoxy-10,11-dimethyl-pyrido[3,4-b]carbazole (0.06 g, 217.1 umol, 1 eq) in DCM (4 mL) was added BBr_3 (271.9 mg, 1.0 mmol, 104.6 uL, 5 eq) at 0°C. The mixture was stirred at 20°C for 1 hr. LC-MS showed 7-methoxy-10,11-dimethyl-10H-pyrido[3,4-b]carbazole was consumed completely and desired mass was detected. The reaction mixture was quenched by addition $NaHCO_3$ 10 mL then concentrated under reduced pressure to give a residue. Then (DCM : MeOH = 10:1) 100 mL was added, filtered and the filtrate was concentrated under reduced pressure to give 10,11-dimethyl-10H-pyrido[3,4-b]carbazol-7-ol.

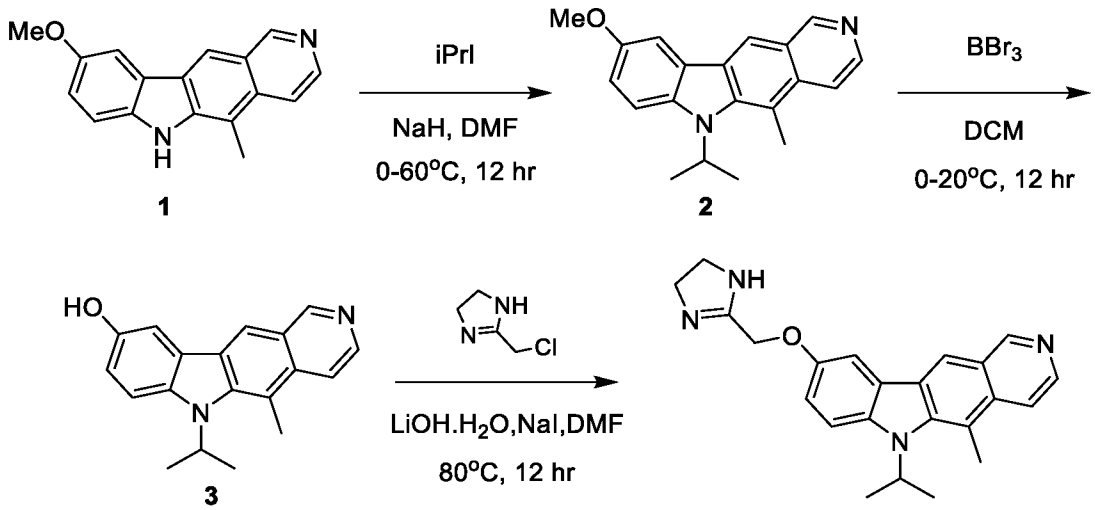
Step 2. 7-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-10,11-dimethyl-10H-pyrido[3,4-b]carbazole

[00253] To a solution of 2-(chloromethyl)-1H-imidazole;hydrochloride (11.6 mg, 76.2 umol, 1 eq) in DMF (3 mL) was added $LiOH.H_2O$ (12.8 mg, 304.9 umol, 4 eq) and 10,11-dimethylpyrido[3,4-b]carbazol-7-ol (20 mg, 76.2 umol, 1 eq), NaI (11.4 mg, 76.2 umol, 1 eq) was added. The mixture was stirred at 75°C for 12 hrs. LC-MS showed 10,11-dimethyl-10H-pyrido[3,4-b]carbazol-7-ol was consumed and desired mass was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 1%-30%,8min) to give 7-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-10,11-dimethyl-pyrido[3,4-b]carbazole.

MS (ESI): m/z = 345.0 $[M+H]^+$

EXAMPLE 84

9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopropyl-5-methyl- pyrido[4,3-b]carbazole



Step 1: 6-isopropyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00254] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (300 mg, 1.1 mmol, 1 eq) in DMF (30 mL) was added NaH (91.5 mg, 2.3 mmol, 60% purity, 2 eq) at 0°C, then was added 2-iodopropane (583.2 mg, 3.4 mmol, 343.1 uL, 3 eq), the mixture was stirred at 60°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was quenched by addition NH_4Cl 50 mL , and then extracted with Ethyl acetate (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-isopropyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole.

6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

[00255] To a solution of 6-isopropyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole (200 mg, 657.1 umol, 1 eq) in DCM (3 mL) was at 0°C added BBr_3 (823.1 mg, 3.3 mmol, 316.5 uL, 5 eq). The mixture was stirred at 20°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was quenched by addition $NaHCO_3$ 10 mL, and extracted with DCM (3 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-isopropyl-5-methyl-pyrido[4,3-b]carbazol-9-ol.

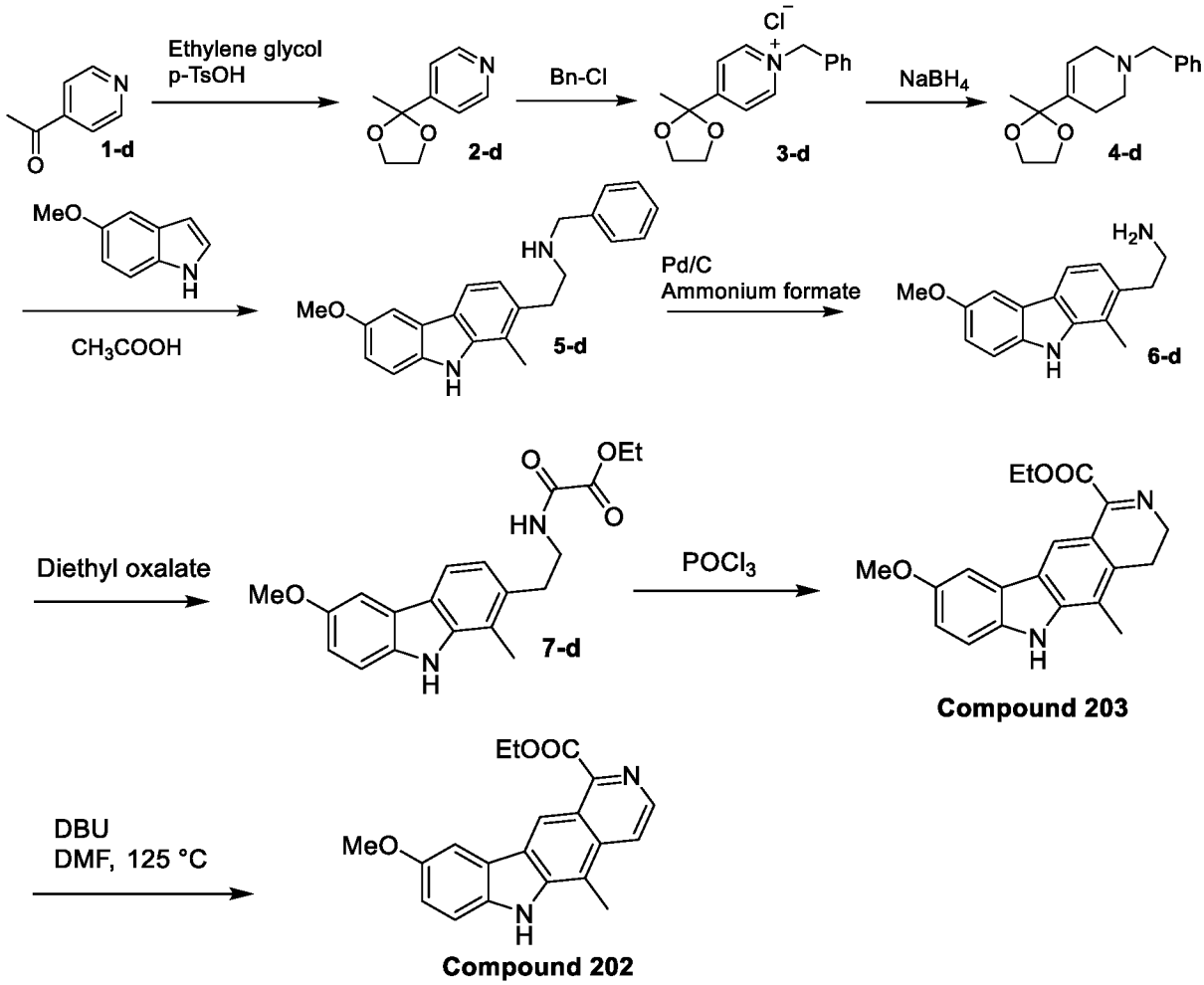
Step 2: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazole

[00256] To a solution of 6-isopropyl-5-methyl-pyrido[4,3-b]carbazol-9-ol (30 mg, 103.3 umol, 1 eq) in DMF (3 mL) were added $LiOH.H_2O$ (17.3 mg, 413.3 umol, 4 eq), 2-

(chloromethyl)-1H-imidazole (15.8 mg, 103.3 umol, 1 eq, HCl) and NaI (15.5 mg, 103.3 umol, 1 eq). The mixture was stirred at 80°C for 12 hrs. LC-MS showed desired compound was detected. The residue was purified by prep-HPLC (FA condition; column: 3_Phenomenex Luna C18 75×30mm×3um; mobile phase: [water(0.2%FA)-ACN]; B%: 1%-30%, 8min) to afford **9**-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopropyl-5-methyl-pyrido[4,3-b]carbazole.

MS (ESI): m/z = 373.1 $[M+H]^+$

[00257] **Synthesis of Compounds 194 and 195**

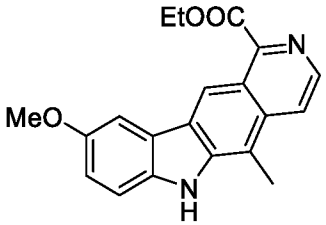


[00258] Compounds **1-d – 4-d** (Besselievre, R. *et al. Tetrahedron* **1981,** *37*, 241-246; Alvarez, M. *et al. Tetrahedron* **1987,** *43* (11), 2513-2522) and **5-d**, **7-d** and **Compound 203** (Jasztold-Howorko, R. *et al. J Med Chem* **1994,** *37* (15), 2445-2452) were synthesized as previously reported.

[00259] **2-(6-methoxy-1-methyl-9*H*-carbazol-2-yl)ethan-1-amine (6-d).** Pd-C (10 wt.%, 192 mg, 0.18 mmol, 0.2 eq) and ammonium formate (255 mg, 4.05 mmol, 4.5 eq) were added to a solution of **5-d** in MeOH (25 mL). The reaction mixture was heated to 70 °C

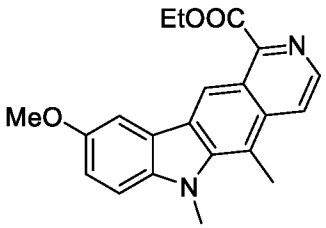
and stirred for 1 hour before it was filtered over Celite and concentrated *in vacuo*. The crude product was purified by flash chromatography (DCM/MeOH 9:1, 1% NH_4OH) providing compound **6-d** (167 mg) in 73% yield. ^1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 6.98 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 2.89 – 2.83 (m, 2H), 2.82 – 2.75 (m, 2H), 2.49 (s, 3H). The spectral characteristics are identical to those previously reported (Jasztold-Howorko, R. (1994)).

[00260] **Ethyl-9-methoxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxylate** (**Compound 202**).



[00261] DBU (131 µL, 1.41 mmol, 2.0 eq) was added to a solution of **Compound 203** (250 mg, 0.705 mmol, 1.0 eq) in DMF (2.3 mL). The reaction mixture was heated to 125 °C and stirred for 90 min. The solvent was evaporated and the concentrated reaction mixture was diluted with DCM/MeOH 9:1 (20 mL) and H_2O (15 mL). The product was extracted with DCM/MeOH 9:1 three times (15 mL), the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1-10% MeOH in DCM, linear gradient) to provide **Compound 202** (105 mg) in 44% yield. ^1H NMR (700 MHz, MeOD) δ 9.26 (s, 1H), 8.30 (dd, *J* = 1.9, 6.6 Hz, 1H), 8.19 (dd, *J* = 1.9, 6.6 Hz, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.16 – 7.11 (m, 1H), 4.75 (q, *J* = 7.2 Hz, 1H), 3.92 (s, 3H), 2.68 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, MeOD) δ 161.24, 154.75, 143.93, 141.47, 137.32, 134.76, 129.05, 128.72, 122.14, 121.37, 118.80, 118.07, 117.31, 111.73, 111.65, 103.96, 63.79, 54.95, 13.05, 11.02.

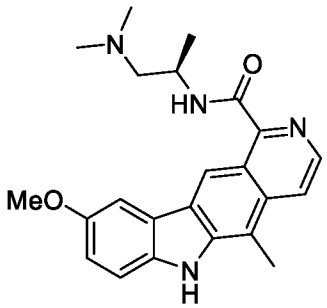
[00262] **Ethyl-9-methoxy-5,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxylate** (**Compound 204**).



[00263] **Compound 202** (120 mg, 0.359 mmol, 1.0 eq) was dissolved in DMF (1.8 mL) and cooled to 0 °C. After the addition of NaH (60% suspension in mineral oil, 19 mg,

0.467 mmol, 1.3 eq) the resulting suspension was stirred for 30 min at 0 °C before methyl iodide (25 µL, 0.395 mmol, 1.1 eq) was added. The cooling bath was removed and the reaction mixture was stirred at room temperature for 12 hours. After the dilution with DCM (15 mL) and H_2O (10 mL) the product was extracted three times with DCM (10 mL). The combined organic extracts were dried over Na2SO4, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (1-10% MeOH in DCM, linear gradient) providing **Compound 204** (73 mg) in 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.62 (d, J = 6.5 Hz, 1H), 8.28 (d, J = 6.5 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.29 – 7.22 (m, 1H), 4.68 (q, J = 7.2 Hz, 2H), 4.17 (s, 3H), 3.98 (s, 3H), 3.12 (s, 3H), 1.57 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.98, 154.21, 141.80, 139.71, 139.51, 135.02, 127.51, 122.97, 121.09, 119.06, 117.05, 115.41, 111.11, 109.45, 103.99, 62.15, 56.21, 33.61, 14.56, 13.85.

[00264] **(*R*)-*N*-(1-(dimethylamino)propan-2-yl)-9-methoxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide** (**Compound 194**).

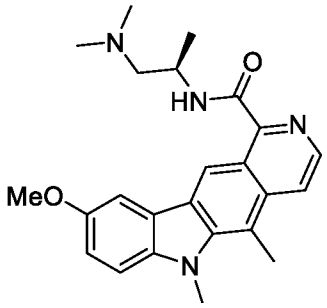


[00265] To a solution of **Compound 202** (25 mg, 0.075 mmol, 1.0 eq) in EtOH (1.5 mL) was added NaOH (225 µL, 0.171 mmol, 3.0 eq) and the mixture was refluxed for 90 min at 83 °C. After neutralization with HCl (1M) the reaction mixture was concentrated *in vacuo* and lyophilized to give the corresponding acid in quantitative yield.

[00266] The acid (21.5 mg, 0.038 mmol, 1.0 eq) was dissolved in DMF (0.5 mL) and EDC (11 mg, 0.056 mmol, 1.5 eq), HOBt (7.6 mg, 0.056 mmol, 1.5 eq) and DIPEA (19 µL, 0.113 mmol, 3.0 eq) were added. The mixture was stirred for 5 min at room temperature before (*R*)-N^1,N^1-dimethylpropane-1,2-diamine (7.7 mg, 0.075 mmol, 2.0 eq) was added. After stirring for 14 hours at room temperature the solvent was evaporated and the product was purified by reversed phase flash chromatography (0-100% MeOH in H_2O, 0.1% TFA, linear gradient) providing **Compound 194** (15 mg) in 79% yield. ^{1}H NMR (700 MHz, MeOD) δ 9.17 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 8.29 (d, *J* = 6.7 Hz, 1H), 7.76 (dd, *J* = 3.8, 7.3 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 3.95 (s, 3H), 3.54 – 3.48 (m, 1H), 3.45 – 3.38 (m, 1H), 3.12 (s, 7H), 3.03 – 2.90 (m, 1H), 2.89 – 2.78 (m, 3H), 1.51 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (176 MHz, MeOD) δ 165.24, 154.69, 150.29, 143.72, 137.65, 134.06, 131.87,

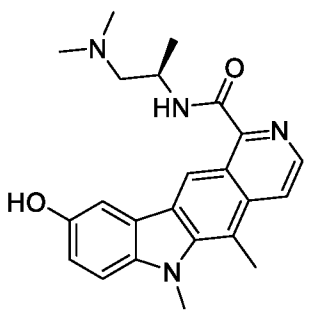
128.07, 122.66, 119.60, 118.51, 117.64, 116.74, 111.68, 104.20, 61.87, 55.04, 41.64, 17.35, 10.94.

[00267] **(*R*)-*N*-(1-(dimethylamino)propan-2-yl)-9-methoxy-5,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide** (**Compound 212**).



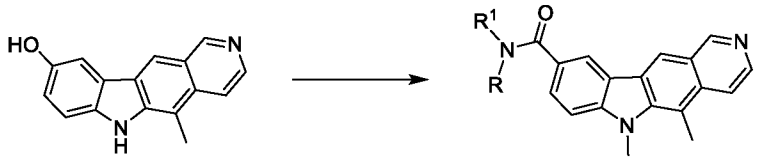
[00268] To a solution of **Compound 204** (20 mg, 0.057 mmol, 1.0 eq) in EtOH (1.5 mL) was added NaOH (171 µL, 0.171 mmol, 3.0 eq) and the mixture was refluxed for 90 min at 83 °C. After neutralization with HCl (1M) the reaction mixture was concentrated *in vacuo* and lyophilized to give the corresponding acid in quantitative yield. The acid (10 mg, 0.022 mmol, 1.0 eq) was dissolved in DMF (0.5 mL) and EDC (6.3 mg, 0.033 mmol, 1.5 eq), HOBt (4.4 mg, 0.033 mmol, 1.5 eq) and DIPEA (11 µL, 0.066 mmol, 3.0 eq) were added. The mixture was stirred for 5 min at room temperature before (*R*)-N^1,N^1-dimethylpropane-1,2-diamine (4.5 mg, 0.044 mmol, 2.0 eq) was added. After stirring for 20 hours at room temperature the solvent was evaporated and the product was purified by reversed phase flash chromatography (0-100% MeOH in H_2O, 0.1% TFA, linear gradient) providing **Compound 212** (7.2 mg) in 63% yield. ^{1}H NMR (700 MHz, MeOD) δ 9.05 (s, 1H), 8.31 (d, *J* = 6.0 Hz, 1H), 8.23 (d, *J* = 6.1 Hz, 1H), 7.64 (s, 1H), 7.32 (dd, *J* = 1.9, 8.8 Hz, 1H), 7.22 – 7.13 (m, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.54 – 3.48 (m, 1H), 3.45 – 3.39 (m, 1H), 3.29 – 3.02 (m, 7H), 2.96 (s, 3H), 1.50 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (176 MHz, MeOD) δ 164.98, 154.84, 149.66, 143.20, 139.43, 135.16, 132.15, 128.38, 121.92, 119.65, 118.50, 117.23, 116.48, 112.16, 109.86, 103.80, 61.77, 55.03, 41.60, 32.53, 17.40, 12.57.

[00269] **(*R*)-*N*-(1-(dimethylamino)propan-2-yl)-9-hydroxy-5,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole-1-carboxamide** (**Compound 195**).



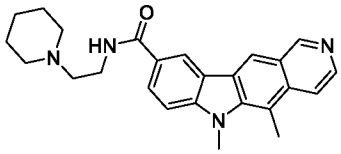
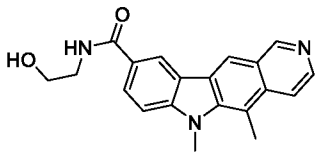
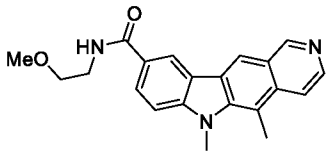
[00270] A solution of **Compound 212** (14 mg, 0.028 mmol, 1.0 eq) in DCM (1.2 mL) was cooled to -70 °C and BBr_3 (1M in DCM, 280 µL, 0.28 mmol, 10 eq) was added. The reaction mixture was allowed to come to room temperature over 5 hours and stirring was continued for further 12 hours. The reaction was quenched by pouring into ice-water (ca. 5 mL) and subsequent basification with NEt_3. After stirring for 3 hours at room temperature the phases were separated and the product was extracted with DCM (3x10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by preparative HPLC (linear gradient 10-100% acetonitrile/MeOH = 1:1, 0.1% TFA, 10 min) providing **Compound 195** (7.7 mg) in 55% yield. ^{1}H NMR (400 MHz, MeOD) δ 9.09 (s, 1H), 8.42 (d, *J* = 6.6 Hz, 1H), 8.34 (d, *J* = 6.6 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.20 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.12 (s, 3H), 3.65 – 3.49 (m, 2H), 3.22 (bs, 7H), 3.10 (s, 3H), 1.60 (d, *J* = 6.7 Hz, 3H).

[00271] **Compounds 213-215**



[00272] General Procedure

[00273] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (140 mg, 0.53 mmol) in DCM (1 ml) and pyridine (100 µL, 1.20 mmol) was added trifluoromethanesulfonic anhydride (280 mg, 1.0 mmol) at 0 °C. The mixture was warmed up to room temperature, then stirred overnight at room temperature. To the mixture was added water and EtOAc, and the organic phase was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in toluene (5 ml) and $Pd(dppf)Cl_2$ (50 mg, 0.05 mmol) and 2,4,6-trichlorophenylformate (225 mg, 1.0 mmol) were added. DBU (150 µL, 1.0 mmol) was then added and the mixture was heated at 80 °C overnight under nitrogen. Aqueous NH_4Cl and DCM were then added and the organic phase was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in THF (1 ml) and the appropriate amine R^1RNH (0.5 mmol) was added and the mixture stirred overnight at room temperature. The crude product was purified with HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the title compounds as shown in the table below:

Compound #	Compound Name	Structure
213	5,6-dimethyl-N-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole-9-carboxamide	
214	N-(2-hydroxyethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	
215	N-(2-methoxyethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide	

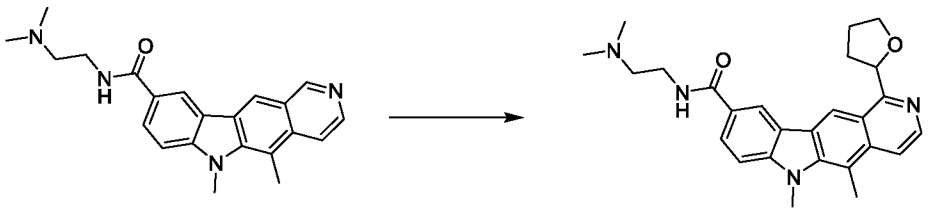
[00274] Analytical data for Compounds 213-215:

[00275] 213: MS (ESI): 401.2 [M+H]+

[00276] 214: MS (ESI): 334.5 [M+H]+

[00277] 215: MS (ESI): 334.1 [M+H]+

[00278] **N-(2-(dimethylamino)ethyl)-5,6-dimethyl-1-(tetrahydrofuran-2-yl)-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 216)**

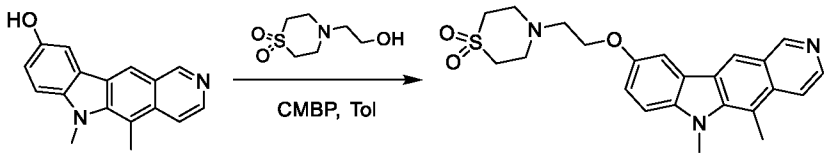


[00279] To a solution of N-(2-(dimethylamino)ethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (3.6 mg, 0.01 mmol) in water (0.1 ml) and MeCN (0.1 ml) was added NHS (11.5 mg, 0.1 mmol) and $NH_4S_2O_8$ (23 mg, 0.1 mmol) at room temperature and the mixture was stirred overnight. The residue was purified by HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H_2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60

min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm.) to afford the desired product.

[00280] MS (ESI): 431.2 [M+H]+

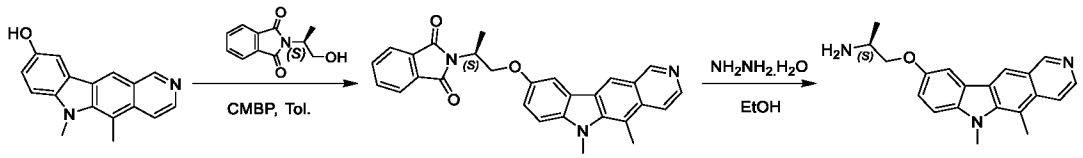
[00281] **4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)thiomorpholine 1,1-dioxide (Compound 217)**



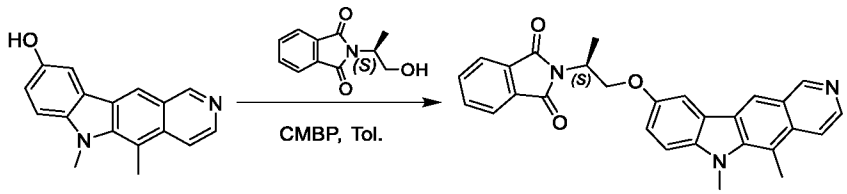
[00282] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 µmol, 1 eq) in toluene (2 mL) was added 2-(1,1-dioxo-1,4-thiazinan-4-yl)ethanol (41.0 mg, 228.7 µmol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (55.2 mg, 228.7 µmol, 1.2 eq) under N_2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was purified by prep-HPLC (TFA condition; column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-45%,9min) to afford 4-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)thiomorpholine 1,1-dioxide.

[00283] MS (ESI): *m/z* = 424.1 $[M+H]^+$

[00284] **(S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine (Compound 218)**



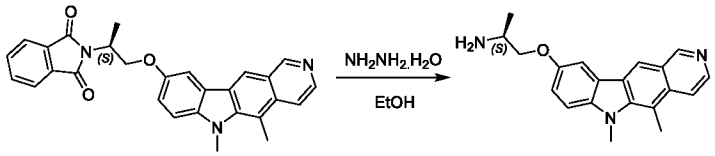
[00285] Step 1: (S)-2-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)isoindoline-1,3-dione



[00286] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (106.5 mg, 406.0 µmol, 1 eq) in toluene (4 mL) was added 2-[(1S)-2-hydroxy-1-methyl-ethyl]isoindoline-1,3-dione (100 mg, 487.3 µmol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (117.6 mg, 487.3 µmol, 1.2 eq) under N_2 atmosphere. The mixture was stirred at 100°C for 2 hr under N_2 atmosphere. LCMS showed the reaction was complete. The reaction mixture was

concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO_2, DCM / MeOH = 10/1) to afford (S)-2-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)isoindoline-1,3-dione.

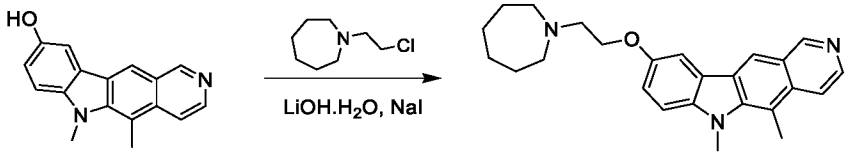
[00287] Step 2: (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine



[00288] To a solution of (S)-2-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl) isoindoline-1,3-dione (150 mg, 333.7 µmol, 1 eq) in EtOH (4 mL) was added $N_2H_4.H_2O$ (34.0 mg, 667.4 µmol, 33.1 µL, 98% purity, 2 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was dissolved in DCM (10 mL) and filtered. The filtrate was concentrated to give the crude product (140 mg) as a yellow solid. The residue (60 mg) was purified by prep-HPLC (TFA condition; column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 4%-34%,9min) to afford (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine.

[00289] MS (ESI): *m/z* = 320.1 $[M+H]^+$

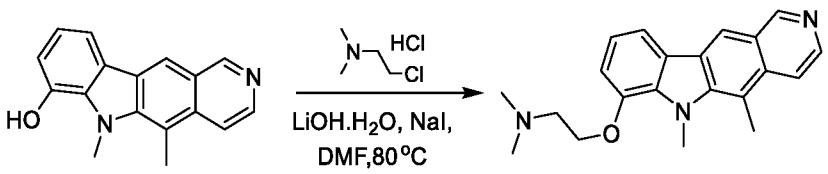
[00290] **9-(2-(azepan-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 219)**



[00291] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 µmol, 1 eq) in DMF (2 mL) was added 1-(2-chloroethyl)azepane (36.9 mg, 228.7 µmol, 1.2 eq), $LiOH.H_2O$ (32.0 mg, 762.4 µmol, 4 eq) and NaI (28.5 mg, 190.6 µmol, 1 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 µm;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-38%,8min) to afford 9-(2-(azepan-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00292] MS (ESI): *m/z* = 388.1 $[M+H]^+$

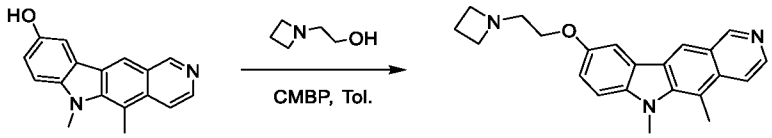
[00293] **5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol (Compound 220)**



[00294] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol (35 mg, 133.4 μmol, 1 eq) in DMF (5 mL) was added 2-chloro-N,N-dimethyl-ethanamine;hydrochloride (23.0 mg, 160.1 μmol, 1.2 eq), $LiOH.H_2O$ (22.4 mg, 533.7 μmol, 4 eq) and NaI (20.0 mg, 133.4 μmol, 1 eq). The mixture was stirred at 80°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (neutral condition; column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 30%-65%,8min.) to give 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-yl)oxy)-N,N-dimethylethanamine.

[00295] MS (ESI): *m/z* = 334.1 $[M+H]^+$

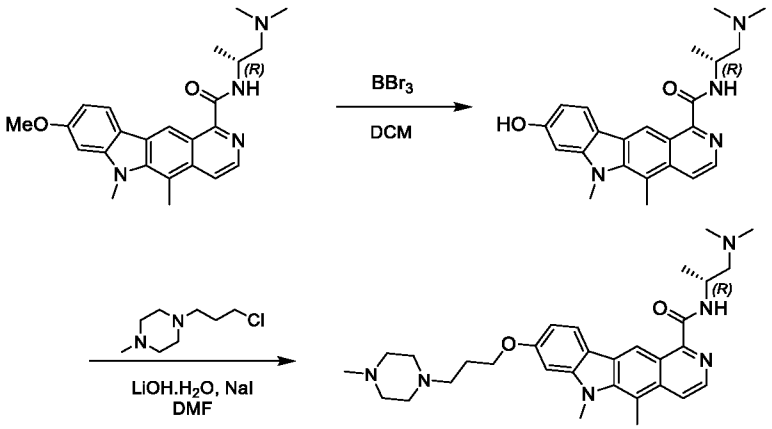
[00296] **9-(2-(azetidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 221)**



[00297] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 μmol, 1 eq) in toluene (2 mL) was added 2-(azetidin-1-yl)ethanol (23.1 mg, 228.7 μmol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (55.2 mg, 228.7 μmol, 1.2 eq) under N_2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-40%,8min) to afford 9-(2-(azetidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00298] MS (ESI): *m/z* = 346.1 $[M+H]^+$

[00299] **(R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-8-(3-(4-methylpiperazin-1-yl)-propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 222)**



[00300] Step 1. (R)-N-(1-(dimethylamino)propan-2-yl)-8-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

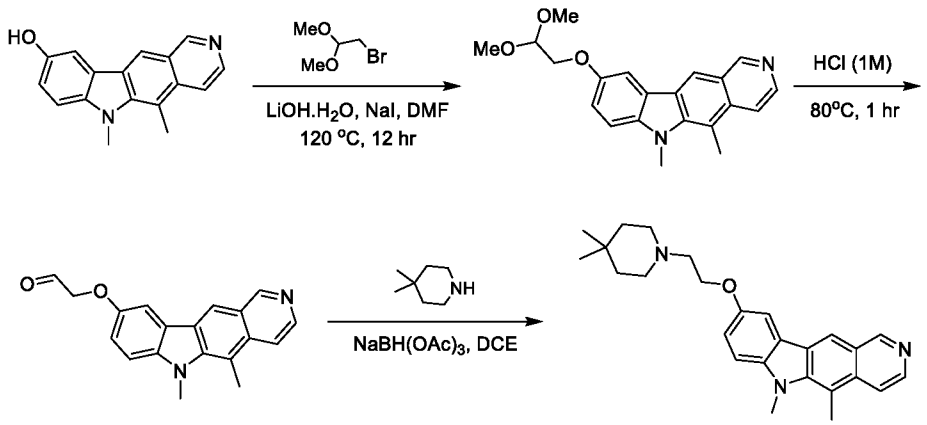
[00301] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-8-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (50 mg, 123.6 μmol, 1 eq) in DCM (2 mL) was added BBr_3 (154.8 mg, 618.0 μmol, 59.5 μL, 5 eq) at 0°C. The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was complete. The reaction was poured into $NH_3.H_2O$ (25% purity, 2 mL) and extracted with DCM (2 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to give (R)-N-(1-(dimethylamino)propan-2-yl)-8-hydroxy-5,6- dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00302] Step 2. (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-8-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00303] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-8-hydroxy-5,6-dimethyl-6H- pyrido[4,3-b]carbazole-1-carboxamide (30 mg, 76.8 μmol, 1 eq) in DMF (2 mL) was added 1-(3-chloropropyl)-4-methyl-piperazine (23.0 mg, 92.1 μmol, 1.2 eq, 2HCl), $LiOH.H_2O$ (12.9 mg, 307.3 μmol, 4 eq) and NaI (11.5 mg, 76.8 μmol, 1 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 μm;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-40%,8min) to afford (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-8-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00304] MS (ESI): *m/z* = 531.2 $[M+H]^+$

[00305] **9-(2-(4,4-dimethylpiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 223)**



[00306] Step 1: 9-(2,2-dimethoxyethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00307] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 μmol, 1 eq) in DMF (4 mL) was added 2-bromo-1,1-dimethoxy-ethane (128.8 mg, 762.4 μmol, 89.4 μL, 2 eq), $LiOH.H_2O$ (63.9 mg, 1.5 mmol, 4 eq) and NaI (57.1 mg, 381.2 μmol, 1 eq). The mixture was stirred at 120°C for 12 hr. LCMS showed the desired product was formed. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=0/1) to afford 9-(2,2-dimethoxyethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00308] Step 2: 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetaldehyde

[00309] A solution of 9-(2,2-dimethoxyethoxy)-5,6-dimethyl-pyrido[4,3-b]carbazole (60.0 mg, 171.2 μmol, 1 eq) in THF (1.5 mL) and HCl (1 M) (1 mL) was heated to 80°C for 2 hr. LCMS showed the reaction was complete. The reaction was added to CH_3CN (10 mL) and yellow solid was precipitated. The solid was filtered and washed with CH_3CN (2 mL × 3) to give 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetaldehyde.

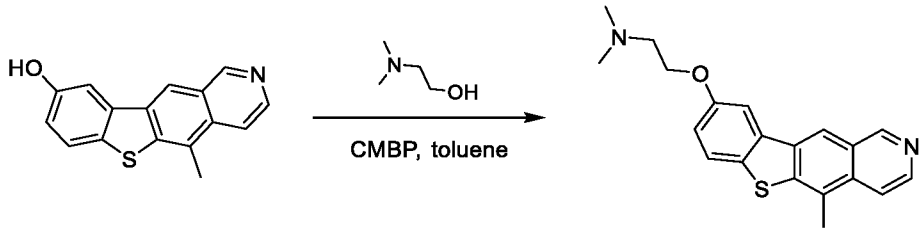
[00310] Step 3: 9-(2-(4,4-dimethylpiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00311] To a solution of 2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxyacetaldehyde (40 mg, 131.4 μmol, 1 eq) in DCE (2 mL) was added 4,4-dimethylpiperidine (23.6 mg, 157.7 μmol, 25.5 μL, 1.2 eq, HCl) and adjusted pH to 7 with TEA, and then added AcOH to adjusted pH to 5. $NaBH(OAc)_3$ (111.4 mg, 525.7 μmol, 4 eq) was added to above mixture and the mixture was stirred at 45°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was purified by prep-HPLC (TFA condition;column: Phenomenex Gemini-NX 150*30mm*5μm;mobile phase: [water(0.1%TFA)-ACN];B%: 4%-34%,9min). The residue was purified by prep-HPLC (neutral condition; column: Waters Xbridge BEH C18 100*25mm*5μm;mobile phase:

[water(10mM NH4HCO3)-ACN];B%: 55%-90%,10min) to afford 9-(2-(4,4-dimethylpiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00312] MS (ESI): *m/z* = 402.1 $[M+H]^+$

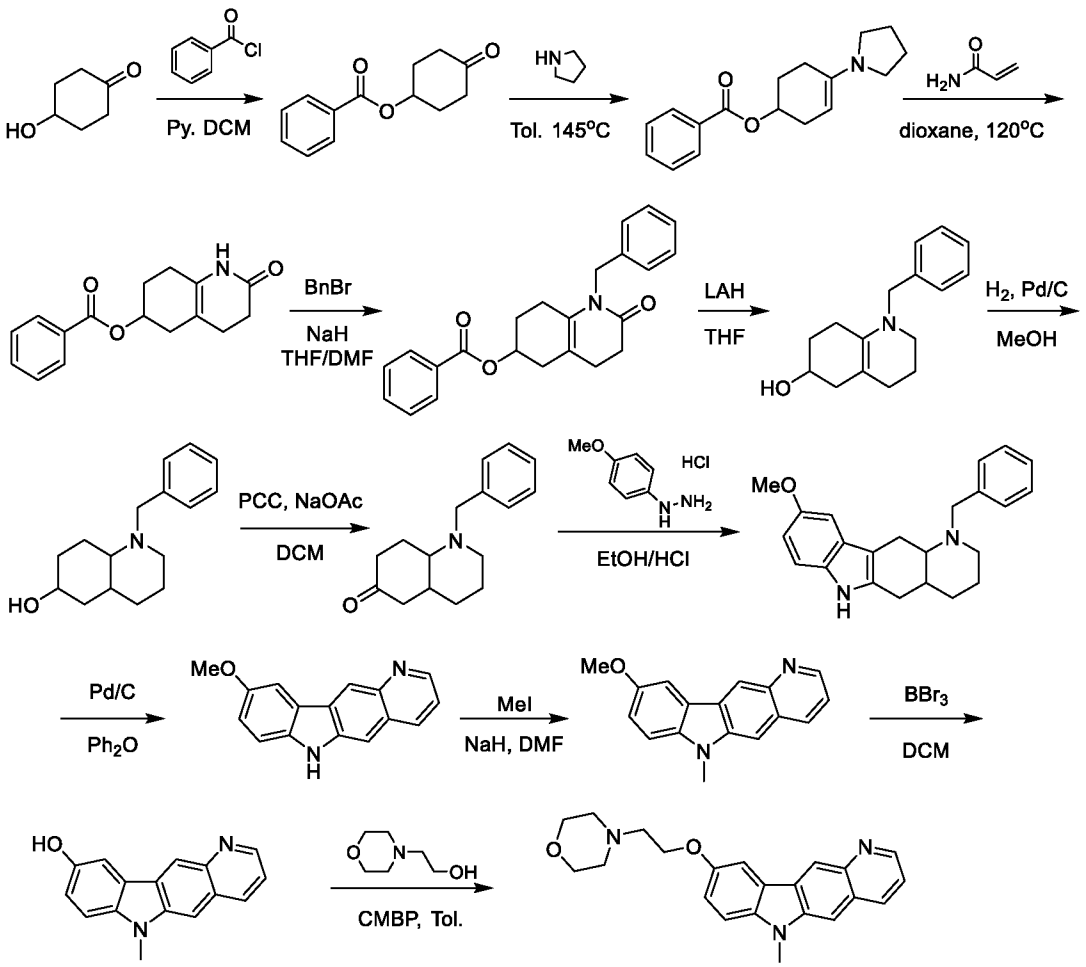
[00313] **N,N-dimethyl-2-((5-methylbenzo[4,5]thieno[2,3-g]isoquinolin-9-yl)oxy)ethanamine (Compound 224)**



[00314] To a solution of 5-methylbenzothiopheno[2,3-g]isoquinolin-9-ol (50 mg, 188.4 μmol, 1 eq) in toluene (2 mL) was added 2-(dimethylamino)ethanol (20.1 mg, 226.1 μmol, 22.7 μL, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (54.5 mg, 226.1 μmol, 1.2 eq) under N_2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue, which was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 μm;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-36%,8min) to afford N,N-dimethyl-2-((5-methylbenzo[4,5]thieno[2,3-g]isoquinolin-9-yl)oxy)ethanamine.

[00315] MS (ESI): *m/z* = 337.1 $[M+H]^+$

[00316] **4-(2-((6-methyl-6H-pyrido[3,2-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 225)**



[00317] Step 1: (4-oxocyclohexyl) benzoate

[00318] To a solution of 4-hydroxycyclohexanone (25 g, 219.0 mmol, 1 eq.) in 500 mL of DCM was added pyridine (41.6 g, 525.7 mmol, 42.4 mL, 2.4 eq.) and benzoyl chloride (37 g, 262.8 mmol, 30.5 mL, 1.2 eq), then the mixture was stirred at 20°C for 12 hr. TLC (Petroleum ether / Ethyl acetate = 1/1) indicated new spots formed. The reaction mixture was diluted with 300 mL of water and then extracted three times with 300 mL of DCM. The combined organic layers were washed with 200 mL of brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether/ethyl acetate = 100/1 to 4/1) to give 4-oxocyclohexyl) benzoate.

[00319] Step 2: 4-(pyrrolidin-1-yl)cyclohex-3-en-1-yl benzoate

[00320] A mixture of (4-oxocyclohexyl) benzoate (21 g, 96.2 mmol, 1 eq.), pyrrolidine (10.3 g, 144.3 mmol, 12.0 mL, 1.5 eq), 4-methylbenzenesulfonic acid (1.7 g, 9.6 mmol, 0.1 eq.) in 20 mL of toluene was stirred at 145°C for 5 hr. HNMR indicated desired compound. The reaction was concentrated under reduced pressure to give 4-(pyrrolidin-1-yl)cyclohex -3-en-1-yl benzoate.

[00321] Step 3: 2-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-6-yl benzoate

[00322] A mixture of 4-(pyrrolidin-1-yl)cyclohex -3-en-1-yl benzoate (26 g, 95.8 mmol, 1 eq.) in 260 mL of dioxane was added prop-2-enamide (17.0 g, 239.5 mmol, 16.5 mL, 2.5 eq.). The mixture was stirred at 120°C for 12 hr. LCMS found the MS of desired compound. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether / ethyl acetate = 100/1 to 3/1) to give 2-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-6-yl benzoate.

[00323] Step 4: 1-benzyl-2-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-6-yl benzoate

[00324] To a solution of 2-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-6-yl benzoate (10 g, 36.9 mmol, 1 eq) in 70 mL of THF and 70 mL of DMF was added NaH (1.5 g, 36.9 mmol, 60% purity, 1 eq) at 0°C. The mixture was stirred at 20°C for 0.5 hr. A solution of BnBr (6.3 g, 36.9 mmol, 4.4 mL, 1 eq.) in 10 mL of THF was added dropwise, the mixture was stirred at 20°C for 3 hr. LCMS found the MS of desired compound. The reaction was diluted with 200 mL of H_2O and then extracted three times with 300 mL of ethyl acetate, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, eluting with a gradient of petroleum ether / ethyl acetate = 100/1 to 7/3) to give 1-benzyl-2-oxo-1,2,3,4,5,6,7,8-octahydroquinolin-6-yl benzoate.

[00325] Step 5: 1-benzyl-1,2,3,4,5,6,7,8-octahydroquinolin-6-ol

[00326] To a solution of (1-benzyl-2-oxo-3,4,5,6,7,8-hexahydroquinolin-6-yl) benzoate (13 g, 36 mmol, 1 eq.) in 150 mL of THF was added $LiAlH_4$ (4.7 g, 123.8 mmol, 3.4 eq.) portion-wise at 0°C, the mixture was stirred at 70°C for 4 hr. LCMS found the MS of desired compound. The reaction was diluted with 5 mL of H_2O, 5 mL of 15% NaOH (aq.) and 15 mL of H_2O, the reaction mixture was stirred 0.5 hr, then the reaction was filtered and concentrated under reduced pressure to give 1-benzyl-1,2,3,4,5,6,7,8-octahydroquinolin-6-ol.

[00327] Step 6: 1-benzyldecahydroquinolin-6-ol

[00328] To a solution of 1-benzyl-1,2,3,4,5,6,7,8-octahydroquinolin-6-ol (5 g, 20.5 mmol, 1 eq) in MeOH (50 mL) was added Pd/C (0.5 g, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15psi) at 25°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel

chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethylacetate/Petroleum ethergradient @ 50 mL/min) to give 1-benzyldecahydroquinolin-6-ol.

[00329] Step 7: 1-benzyloctahydroquinolin-6(2H)-one

[00330] To a solution of 1-benzyldecahydroquinolin-6-ol (4.2 g, 17.12 mmol, 1 eq) in DCM (50 mL) were added PCC (8.0 g, 37.4 mmol, 2.1 eq) and NaOAc (3.0 g, 37.5 mmol, 2.1 eq). The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate /Petroleum ether gradient @ 80 mL/min) to give 1-benzyloctahydroquinolin-6(2H)-one.

[00331] Step 8: 1-benzyl-9-methoxy-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[3,2-b]carbazole

[00332] A mixture of (4-methoxyphenyl)hydrazine (387.5 mg, 2.2 mmol, 1 eq, HCl), 1-benzyloctahydroquinolin-6(2H)-one (540 mg, 2.2 mmol, 1 eq), HCl (12 M, 216.3 uL, 1.1 eq) in EtOH (10 mL) was stirred at 20°C for 12 hr under N_2. LCMS showed the reaction was completed and desired product was detected. The mixture was filtered and washed with EtOH (10 mL × 2) and collected the solid to get product. The product was diluted with $NaHCO_3$ (50 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). The residue was purified by prep-TLC (SiO_2, Petroleum ether : Ethyl acetate = 2:1) to afford 1-benzyl-9-methoxy-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[3,2-b]carbazole.

[00333] Step 9: 9-methoxy-6H-pyrido[3,2-b]carbazole

[00334] To a solution of 1-benzyl-9-methoxy-2,3,4,4a,5,6,11,11a-octahydro-1H-pyrido[3,2-b]carbazole (260.0 mg, 759.2 umol, 1 eq) in Ph_2O (5 mL) was added Pd/C (60 mg, 10% purity). The mixture was stirred at 220°C for 1 hr under N_2. LCMS showed the reaction was completed and desired product was detected. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate / Petroleum ether gradient to Eluent of 0~10% Methanol / Dichloromethane@ 60mL/min) to give 9-methoxy-6H-pyrido[3,2-b]carbazole.

[00335] Step 10: 9-methoxy-6-methyl-pyrido[3,2-b]carbazole

[00336] To a solution of 9-methoxy-6H-pyrido[3,2-b]carbazole (130 mg, 523.6 umol, 1 eq) in THF (10 mL) was added NaH (62.8 mg, 1.5 mmol, 60% purity, 3 eq) and MeI (70.6 mg, 497.4 umol, 30.9 uL, 0.95 eq) at 0°C. Then the mixture was stirred at 25°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into NH_4Cl (10 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 9-methoxy-6-methyl-pyrido[3,2-b]carbazole.

[00337] Step 11: 6-methyl-6H-pyrido[3,2-b]carbazol-9-ol

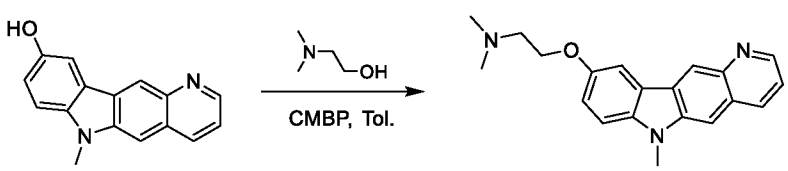
[00338] To a solution of 9-methoxy-6-methyl-pyrido[3,2-b]carbazole (140 mg, 533.7 umol, 1 eq) in DCM (10 mL) was added BBr_3 (267.4 mg, 1.0 mmol, 102.8 uL, 2 eq) at 0°C. Then the mixture was stirred at 0°C for 2 hr. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into $NaHCO_3$ (50 mL) and extracted with DCM (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-methyl-6H-pyrido[3,2-b]carbazol-9-ol.

[00339] Step 12: 4-[2-(6-methylpyrido[3,2-b]carbazol-9-yl)oxyethyl]morpholine

[00340] To a solution of 6-methylpyrido[3,2-b]carbazol-9-ol (50 mg, 201.3 umol, 1 eq) in Tol. (2 mL) was added 2-morpholinoethanol (31.7 mg, 241.6 umol, 29.6 uL, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (58.3 mg, 241.6 umol, 1.2 eq) under N2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-33%,8min) to afford 4-[2-(6-methylpyrido[3,2-b]carbazol-9-yl)oxyethyl]morpholine.

[00341] MS (ESI): m/z = 362.1 [M+H]+

[00342] **N,N-dimethyl-2-((6-methyl-6H-pyrido[3,2-b]carbazol-9-yl)oxy)ethanamine (Compound 226)**

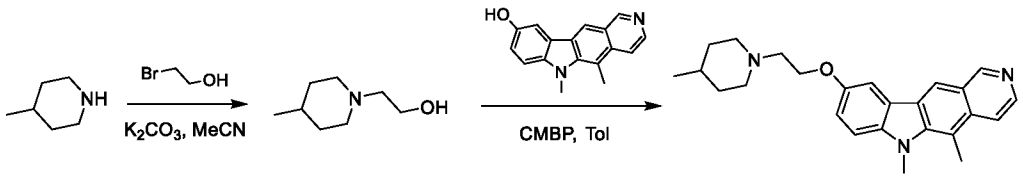


[00343] To a solution of 6-methylpyrido[3,2-b]carbazol-9-ol (50 mg, 201.3 μmol, 1 eq) in Tol. (2 mL) was added 2-(dimethylamino)ethanol (21.5 mg, 241.6 μmol, 24.2 μL, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (72.9 mg, 302.0 μmol, 1.5 eq) under N_2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was completely. The

reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition;column: Phenomenex luna C18 100*40mm*5 μm;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,8min) to afford N,N-dimethyl-2-(6-methylpyrido[3,2-b]carbazol-9-yl)oxy-ethanamine.

[00344] MS (ESI): m/z = 320.1 [M+H]+

[00345] **5,6-dimethyl-9-(2-(4-methylpiperidin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole (Compound 227)**



[00346] Step 1: 2-(4-methylpiperidin-1-yl)ethanol

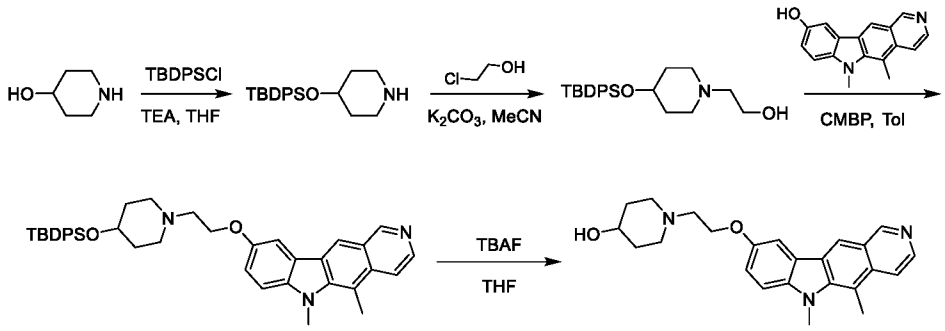
[00347] To a solution of 4-methylpiperidine (1 g, 10.0 mmol, 1.1 mL, 1 eq) in MeCN (10.0 mL) was added K_2CO_3 (4.1 g, 30.2 mmol, 3 eq) 2-bromoethanol (1.3 g, 11.0 mmol, 787.5 μL, 1.1 eq). The mixture was stirred at 25°C for 12 hrs. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(4-methylpiperidin-1-yl)ethanol.

[00348] Step 2: 5,6-dimethyl-9-(2-(4-methylpiperidin-1-yl)ethoxy)-6H-pyrido[4,3-b]carbazole

[00349] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 μmol, 1 eq) in toluene (2.0 mL) was added 2-(4-methylpiperidin-1-yl)ethanol (54.6 mg, 381.2 μmol, 2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (55.2 mg, 228.7 μmol, 1.2 eq). The mixture was stirred at 100°C for 12 hrs under N_2. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition column: Phenomenex Gemini-NX C18 75*30mm*3μm;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,8min) to afford 5,6-dimethyl-9-[2-(4-methyl- 1-piperidyl)ethoxy]pyrido[4,3-b]carbazole.

[00350] MS (ESI): *m/z* = 388.1 $[M+H]^+$

[00351] **1-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)piperidin-4-ol (Compound 228)**



[00352] Step 1: 4-((tert-butyldiphenylsilyl)oxy)piperidine

[00353] To a solution of piperidin-4-ol (2 g, 19.7 mmol, 1 eq) in THF (50.0 mL) was added TEA (6.0 g, 59.3 mmol, 8.2 mL, 3 eq), TBDPSCl (7.9 g, 29.0 mmol, 7.4 mL, 1.4 eq). The mixture was stirred at 25°C for 12 hrs. LCMS showed the reaction was completed and desired product. The mixture was concentrated to get crude residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate / Petroleum ether gradient @ 60 mL/min) to afford 4-((tert-butyldiphenylsilyl)oxy)piperidine.

[00354] Step 2: 2-(4-((tert-butyldiphenylsilyl)oxy)piperidin-1-yl)ethanol

[00355] To a solution of 4-((tert-butyldiphenylsilyl)oxy)piperidine (2.3 g, 6.7 mmol, 1 eq) in MeCN (20.0 mL) was added K_2CO_3 (4.6 g, 33.8 mmol, 5 eq), 2-bromoethanol (1.6 g, 13.5 mmol, 961.9 uL, 2 eq). The mixture was stirred at 25°C for 12 hrs. LCMS showed the reaction was completed and desired product. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(4-((tert-butyldiphenylsilyl)oxy) piperidin-1-yl)ethanol.

[00356] Step 3: 9-(2-(4-((tert-butyldiphenylsilyl)oxy)piperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

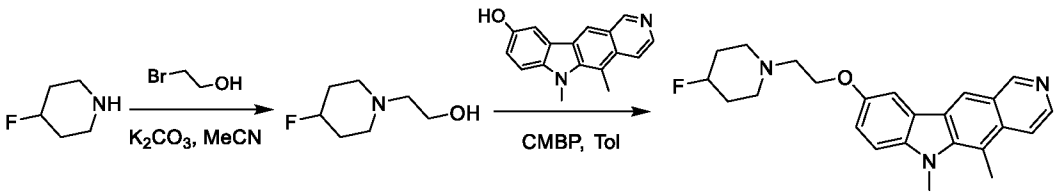
[00357] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 µmol, 1 eq) in toluene (4 mL) was added 2-(4-((tert-butyldiphenylsilyl)oxy) piperidin-1-yl)ethanol (146.2 mg, 381.2 µmol, 2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (55.2 mg, 228.7 µmol, 1.2 eq). The mixture was stirred at 100°C for 12 hrs under N_2. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue, which was purified by prep-TLC (SiO_2, DCM / MeOH = 10/1) to afford 9-(2-(4-((tert-butyldiphenylsilyl) oxy)piperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00358] Step 4; 1-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)piperidin-4-ol

[00359] To a solution of 9-(2-(4-((tert-butyldiphenylsilyl)oxy)piperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (100 mg, 159.2 μmol, 1 eq) in THF (2.0 mL) was added TBAF (1 M, 318.5 μL, 2 eq, in THF). The mixture was stirred at 50°C for 12 hr. LCMS the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX C18 75*30mm*3μm;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,8min) to afford 1-(2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)piperidin-4-ol.

[00360] MS (ESI): *m/z* = 390.1 $[M+H]^+$

[00361] **9-(2-(4-fluoropiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 229)**



[00362] Step 1: 2-(4-fluoropiperidin-1-yl)ethanol

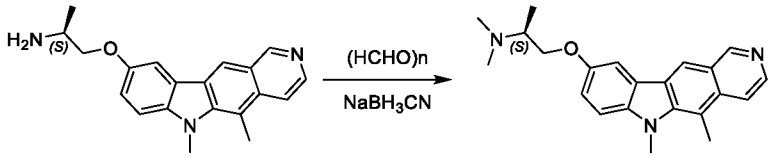
[00363] To a solution of 4-fluoropiperidine (1.0 g, 7.1 mmol, 1 eq, HCl) in ACN (30 mL) was added K_2CO_3 (4.9 g, 35.8 mmol, 5 eq) and 2-bromoethanol (1.7 g, 14.3 mmol, 1.0 mL, 2 eq). The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to remove the solvent. The residue was dissolved in ethyl acetate (20 mL) and washed with H_2O (20 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give 2-(4-fluoropiperidin-1-yl)ethanol.

[00364] 9-(2-(4-fluoropiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00365] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 μmol, 1 eq) in toluene (2 mL) was added 2-(4-fluoro-1-piperidyl)ethanol (33.6 mg, 228.7 μmol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (55.2 mg, 228.7 μmol, 1.2 eq) under N_2. The mixture was stirred at 100°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5μm;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-40%,8min) to afford 9-(2-(4-fluoropiperidin-1-yl)ethoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00366] MS (ESI): *m/z* = 392.1 $[M+H]^+$

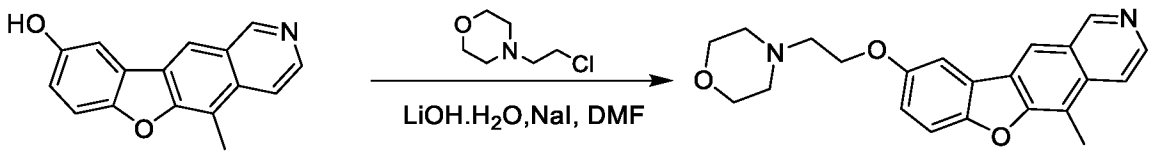
[00367] **(S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylpropan-2-amine (Compound 230)**



[00368] To a solution of (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan- 2-amine (60 mg, 187.8 μmol, 1 eq) and (HCHO)n (90.1 mg, 939.2 μmol, 5 eq) in MeOH (2 mL) was added AcOH (11.2 mg, 187.8 μmol, 10.7 μL, 1 eq) to adjust pH to 5. Then $NaBH_3CN$ (47.2 mg, 751.4 μmol, 4 eq) was added to the above mixture. The mixture was stirred at 40°C for 12 hr. LCMS showed the reaction was complete. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition;column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,8min). The residue was purified by prep-HPLC (basic condition;column: Waters Xbridge Prep OBD C18 150*40mm*10μm;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 23%-53%,8min) to afford (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylpropan-2-amine.

[00369] MS (ESI): *m/z* = 348.1 $[M+H]^+$

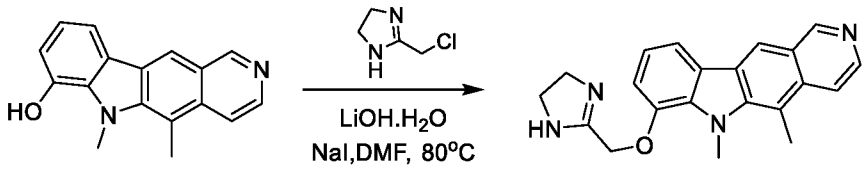
[00370] **5-methyl-9-(2-morpholinoethoxy)benzofuro[2,3-g]isoquinoline (Compound 231)**



[00371] To a solution of 5-methylbenzofuro[2,3-g]isoquinolin-9-ol (70 mg, 280.8 μmol, 1 eq) in DMF (2 mL) was added 4-(2-chloroethyl)morpholine (46.2 mg, 308.9 μmol, 5.4 uL, 1.1 eq), $LiOH.H_2O$ (47.1 mg, 1.1 mmol, 4 eq) and NaI (42.0 mg, 280.8 μmol, 1 eq). The mixture was stirred at 80°C for 12 hrs. LCMS showed most desired product was formed. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition, column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(0.2% FA)-ACN];B%: 1%-40%,8min) to give 5-methyl-9-(2-morpholinoethoxy)benzofuro[2,3-g]isoquinoline.

[00372] MS (ESI): *m/z* = 363.1 $[M+H]^+$

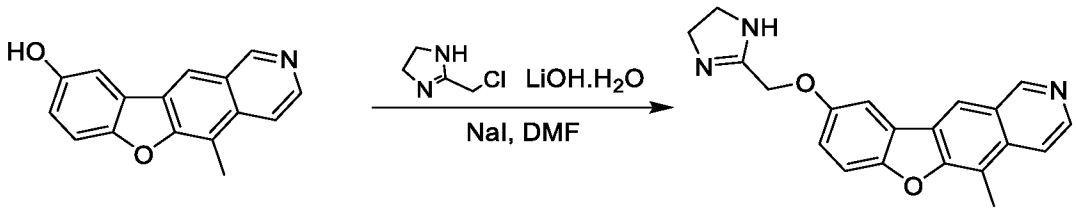
[00373] **7-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 232)**



[00374] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-7-ol (50 mg, 190.6 μmol, 1 eq) in DMF (5 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (35.4 mg, 228.7 μmol, 1.2 eq, HCl), $LiOH.H_2O$ (32.0 mg, 762.4 μmol, 4 eq) and NaI (28.5 mg, 190.6 μmol, 1 eq), the mixture was stirred at 80°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 μm;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-33%,8min) to give 7-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00375] MS (ESI): m/z = 345.1 [M+H]+

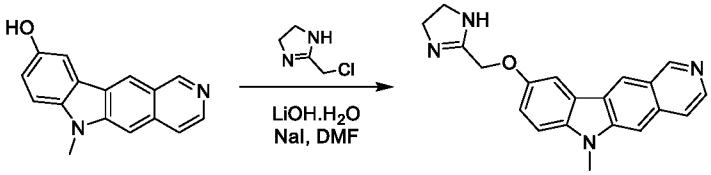
[00376] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methylbenzofuro[2,3-g]isoquinoline (Compound 233)**



[00377] To a solution of 5-methylbenzofuro[2,3-g]isoquinolin-9-ol (70 mg, 280.8 μmol, 1 eq) in DMF (4 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (65.3 mg, 421.2 μmol, 5.4 uL, 1.5 eq, HCl), NaI (42.0 mg, 280.8 μmol, 1 eq) and $LiOH.H_2O$ (47.1 mg, 1.1 mmol, 4 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (FA condition, column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.2%FA)-ACN];B%: 1%-20%,10min) to give 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methylbenzofuro[2,3-g]isoquinoline.

[00378] MS (ESI): *m/z* = 332.0 $[M+H]^+$

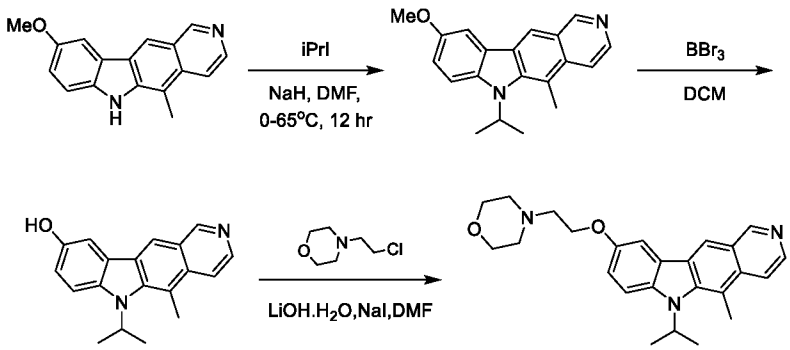
[00379] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-methyl-6H-pyrido[4,3-b]carbazole (Compound 234)**



[00380] To a solution of 6-methylpyrido[4,3-b]carbazol-9-ol (50 mg, 201.3 μmol, 1 eq) in DMF (2.0 mL) were added LiOH.H_2O (33.8 mg, 805.5 μmol, 4 eq) and NaI (30.1 mg, 201.3 μmol, 1 eq) 2-(chloromethyl)-4,5-dihydro-1H-imidazole (46.8 mg, 302.0 μmol, 1.5 eq, HCl). The mixture was stirred at 70°C for 12 hrs. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-30%,7min) to afford 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-methyl-6H-pyrido[4,3-b]carbazole.

[00381] MS (ESI): *m/z* = 331.1 $[M+H]^+$

[00382] **4-(2-((6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 235)**



[00383] Step 1: 6-isopropyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00384] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (200 mg, 762.4 μmol, 1 *eq*) in DMF (5 mL) was added NaH (91.5 mg, 2.2 mmol, 60% purity, 3 eq) and 2-iodopropane (388.8 mg, 2.2 mmol, 228.7 μL, 3 *eq*) at 0°C. Then the mixture was stirred at 65°C for 12 hrs. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into NH_4Cl (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (10 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give 6-isopropyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole.

[00385] Step 2: 6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

[00386] To a solution of 6-isopropyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (110 mg, 361.3 μmol, 1 eq) in DCM (4 mL) was added BBr_3 (452.6 mg, 1.8 mmol, 174.1 μL, 5 eq) at 0°C. The mixture was stirred at 20°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was washed with $NH_3.H_2O$ (20 mL, 25%

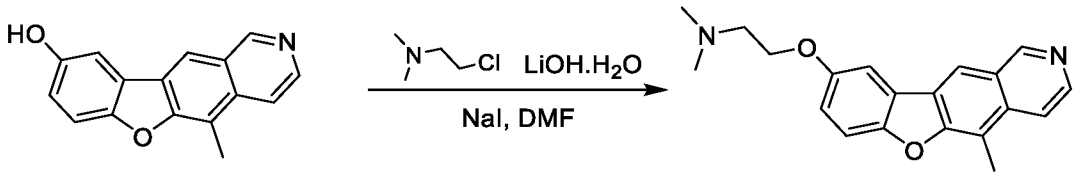
purity) and filtered and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give 6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol.

[00387] Step 3: 4-(2-((6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine

[00388] To a solution of 6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 172.2 µmol, 1 eq) in DMF (2 mL) was added 4-(2-chloroethyl)morpholine (38.4 mg, 206.6 µmol, 1.2 eq, HCl), $LiOH.H_2O$ (28.9 mg, 688.8 µmol, 4 eq) and NaI (25.8 mg, 172.2 µmol, 1 eq). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 µm;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-40%,8min) to give 4-(2-((6-isopropyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine.

[00389] MS (ESI): *m/z* = 404.2 $[M+H]^+$

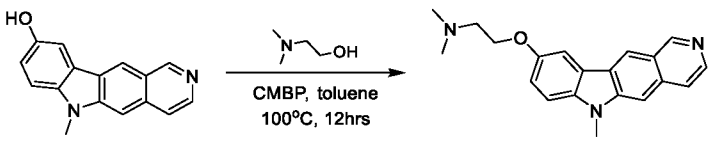
[00390] **N,N-dimethyl-2-((5-methylbenzofuro[2,3-g]isoquinolin-9-yl)oxy)ethanamine (Compound 236)**



[00391] To a solution of 5-methylbenzofuro[2,3-g]isoquinolin-9-ol (60 mg, 240.7 µmol, 1 eq) in DMF (4 mL) was added 2-chloro-N,N-dimethyl-ethanamine (41.6 mg, 288.8 µmol, 5.4 µL, 1.2 eq, HCl) NaI (36.0 mg, 240.7 µmol, 1 eq) and $LiOH.H_2O$ (40.4 mg, 962.8 µmol, 4 eq). The mixture was stirred at 80°C for 12 hr. LCMS showed the reaction was completed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by *prep*-HPLC (FA condition, column: Phenomenex Luna C18 200*40mm*10um;mobile phase: [water(0.2%FA)-ACN];B%: 1%-30%,8min) to give N,N-dimethyl-2-((5-methylbenzofuro[2,3-g]isoquinolin-9-yl)oxy)ethanamine.

[00392] MS (ESI): *m/z* = 321.0 $[M+H]^+$

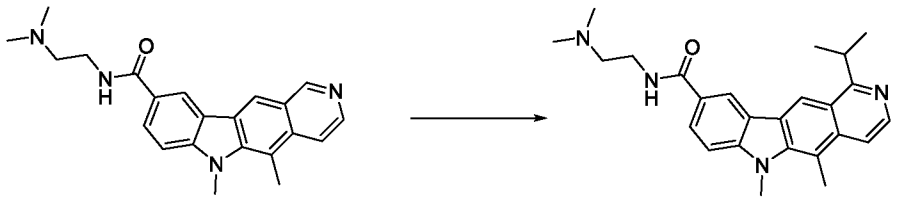
[00393] **N,N-dimethyl-2-((6-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine (Compound 237)**



[00394] To a solution of 6-methylpyrido[4,3-b]carbazol-9-ol (70 mg, 281.9 μmol, 1 eq) in toluene (2.0 mL) were added 2-(dimethylamino)ethanol (25.1 mg, 281.9 μmol, 28.3 μL, 1.0 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (136.0 mg, 563.8 μmol, 2 eq. The mixture was stirred at 100°C for 12 hrs. LCMS showed the reaction was completed and desired product was detected. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 μm;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-22%,8min) to afford N,N-dimethyl-2-(6-methylpyrido[4,3-b] carbazol-9-yl)oxy-ethanamine.

[00395] MS (ESI): *m/z* = 320.1 $[M+H]^+$

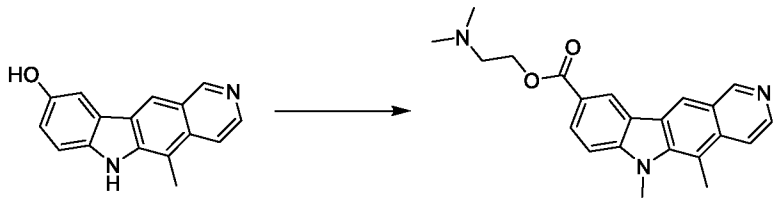
[00396] **N-(2-(dimethylamino)ethyl)-1-isopropyl-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 238)**



[00397] To the solution of N-(2-(dimethylamino)ethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (18 mg, 0.05 mmol) oxalate isopropyl ester (0.1 mmol) in DMSO (0.5 ml) and water (0.1 ml) was added (NH4)S2O8 (22 mg, 0.1 mmol) and the mixture was heated at 50 °C overnight and purified by HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 μm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 μm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the product.

[00398] MS (ESI): 403.5 [M+H]+

[00399] **2-(dimethylamino)ethyl 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylate (Compound 239)**

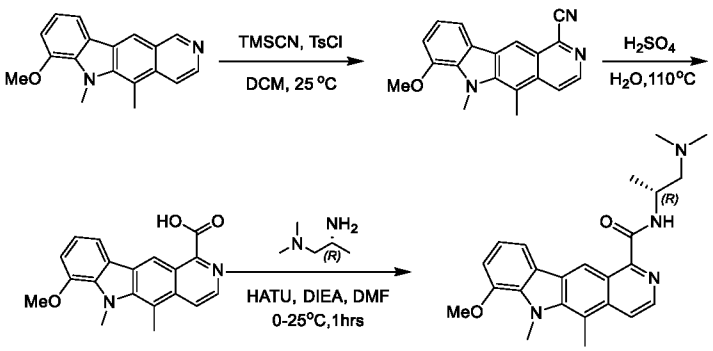


[00400] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (26.4 mg, 0.1 mmol) in DCM (0.2 ml) and pyridine (20 uL, 0.23 mmol) was added trifluoromethanesulfonic

anhydride (53 mg, 0.2 mmol) at 0 °C. The mixture was warmed up to room temperature, then stirred overnight at room temperature. To the mixture was added water and EtOAc, and the org phase was washed with aqueous NaHCO3 and brine, dried over Na2SO4 and concentrated. The residue was dissolved in toluene (1 ml) and Pd(dppf)Cl2 (9.5 mg, 0.01 mmol) and 2,4,6-trichlorophenylformate (42 mg, 0.2 mmol) were added. DBU (28 uL, 0.2 mmol) was then added and the mixture was heated at 80 °C overnight under nitrogen. Aqueous NH4Cl and DCM were then added and the org phase was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was dissolved in water/EtOH (1:1) and LiOH•H2O (42 mg, 1.0 mmol) was added. The mixture was stirred at 60 °C overnight and then purified with RP-HPLC. The resulting carboxylic acid intermediate was dissolved in dichloromethane (1 ml). 2-dimethylaminoethanol (20 uL, 0.2 mmol), DMAP (12 mg, 0.1 mmol) and EDC (38 mg, 0.2 mmol) were added. The mixture was stirred overnight at room temperature and then purified by HPLC (Waters 1525 binary preparatory HPLC system with a gradient elution of mobile phases A and B of the following specifications. Guard column: Atlantis T3 Prep Guard Cartridge (5 µm, 19 mm x 10 mm) Column: Atlantis T3 Prep OBD (100Å, 5 µm, 19 mm x 150 mm) Mobile phase: A= 0.1% TFA in H2O and B= MeOH or ACN; Flow rate: 5 mL/min, Injection volume: 4 mL, Runtime: 60 min, gradient: variable concentrations of B in A; UV detection at 220 & 345 nm) to afford the title compound.

[00401] MS (ESI): 362.2 [M+H]+

[00402] **(R)-N-(1-(dimethylamino)propan-2-yl)-7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 240)**



[00403] Step 1: 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00404] To a solution of 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (200 mg, 723.7 µmol, 1 eq) in DCM (6 mL) was added trimethylsilylformonitrile (186.6 mg, 1.8 mmol, 235.4 µL, 2.6 eq), then TosCl (262.1 mg, 1.3 mmol, 1.9 eq) in DCM (6 mL) was dropwsie added to the above mixture at 25°C. The mixture was stirred at 25°C for 12 hrs. Then LCMS showed intermediate was detected and 2 mL KOH (50% W/W) was added. The mixture was stirred at 25°C for 2 hrs. LC-MS showed desired compound was detected. The

reaction mixture was partitioned between H_2O 15 mL and CH_2Cl_2 15 mL. The aqueous phase was separated, washed with CH_2Cl_2 (10 mL × 2), the organic was phase dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

[00405] Step 2: 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

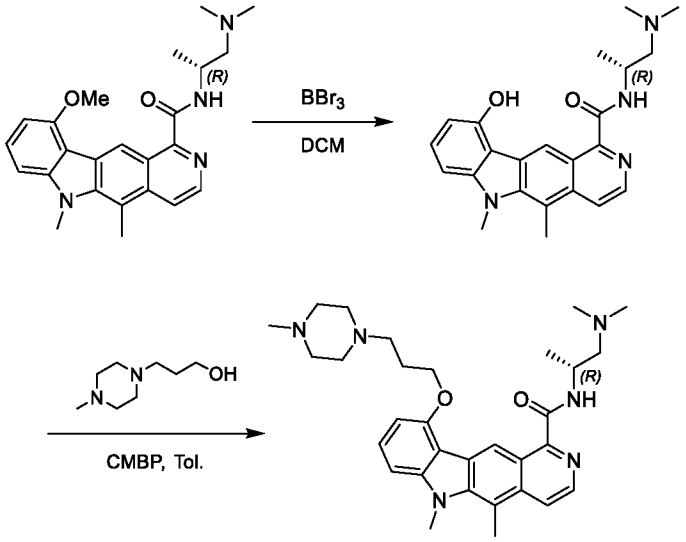
[00406] A solution of 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (200 mg, 663.7 µmol, 1 eq) in H_2SO_4 (2 mL, 98% purity) and H_2O (2 mL) was stirred at 110°C for 12 hrs. LC-MS showed desired compound was detected. The mixture was poured into $NaHCO_3$ (100 mL) and yellow solid was separate out. Then the mixture was filtered and collect the solid to afford 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

[00407] Step 3: (R)-N-(1-(dimethylamino)propan-2-yl)-7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00408] To a solution of 7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 156.0 µmol, 1 eq) in DMF (4 mL) was added (2R)-N1,N1-dimethylpropane-1,2-diamine (81.9 mg, 468.2 µmol, 3 eq, 2 HCl), DIEA (100.8 mg, 780.4 µmol, 135.9 µL, 5 eq) and HATU (118.70 mg, 312.17 µmol, 2 eq) at 0°C. The mixture was stirred at 25°C for 1 hr. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 40%-70%,10min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00409] MS (ESI): *m/z* = 405.1 $[M+H]^+$

[00410] **(R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-10-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 241)**



[00411] Step 1: (R)-N-(1-(dimethylamino)propan-2-yl)-10-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

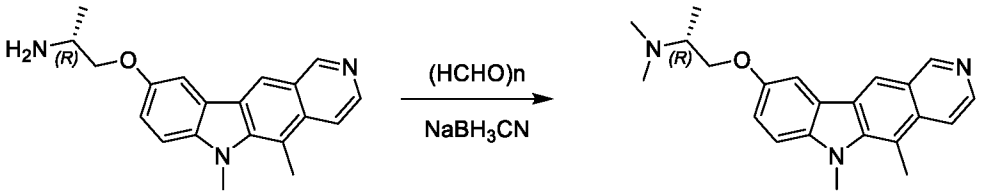
[00412] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-10-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (50 mg, 123.6 umol, 1 eq) in DCM (2.5 mL) was added BBr3 (154.8 mg, 618.0 umol, 59.5 uL, 5 eq) at 0°C. The mixture was stirred at 20°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was add to NH3.H2O(10 mL, 25% purity) and filtered. The filter cake was washed with 10 mL of H2O, dried in vacuum to give (R)-N-(1-(dimethylamino)propan-2-yl)-10-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00413] Step 2: (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-10-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00414] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-10-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (30 mg, 76.8 umol, 1 eq) in Tol. (2 mL) was added 3-(4-methylpiperazin-1-yl)propan-1-ol (14.5 mg, 92.1 umol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (37.0 mg, 153.6 umol, 2 eq) under N2. The mixture was stirred at 100°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,9min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-10-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00415] MS (ESI): m/z = 531.3M+H]+

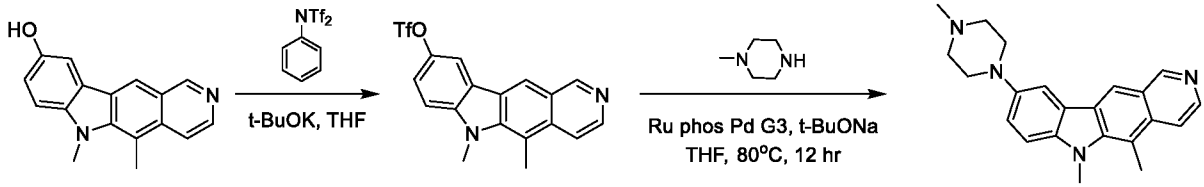
[00416] **(R)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylpropan-2-amine (Compound 242)**



[00417] To a solution of (R)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-amine (80 mg, 250.4 umol, 1 *eq*) and (HCHO)n (120.2 mg, 1.25 mmol, 5 *eq*) in MeOH (4 mL) was added AcOH (15.0 mg, 250.4 μmol, 14.3 μL, 1 *eq*) to adjusted pH to 5. Then $NaBH_3CN$ (62.9 mg, 1.0 mmol, 4 *eq*) was added to the above mixture. The mixture was stirred at 25°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give crude product. The residue was purified by prep-HPLC (basic condition, column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.1%TFA)-ACN];B%: 30%-50%,8min) to give (R)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylpropan-2-amine.

[00418] MS (ESI): *m/z* = 348.1$[M+H]^+$

[00419] **5,6-dimethyl-9-(4-methylpiperazin-1-yl)-6H-pyrido[4,3-b]carbazole (Compound 243)**



[00420] Step 1: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate

[00421] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (269 mg, 1.0 mmol, 1 *eq*) in THF (7 mL) was added t-BuOK (230.1 mg, 2.0 mmol, 2 *eq*) at 0 C. The mixture was stirred at 0°C for 10 min. And then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)-methanesulfonamide (439.6 mg, 1.2 mmol, 1.2 *eq*) was added to the above mixture. The mixture was stirred at 25°C for 12 hr. LCMS showed desired compound was detected. The reaction mixture was partitioned between H_2O 100 mL and EtOAc (50 mL × 3). And the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ethergradient @75 mL/min) to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate.

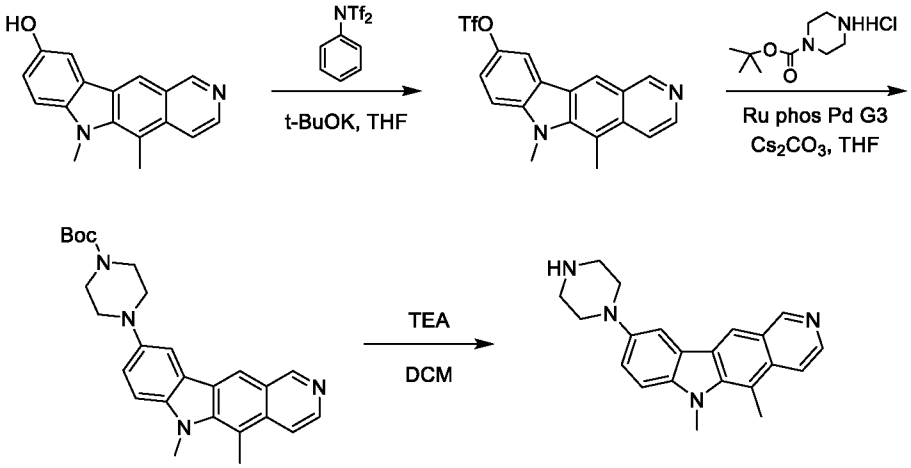
[00422] Step 2: 5,6-dimethyl-9-(4-methylpiperazin-1-yl)-6H-pyrido[4,3-b]carbazole

[00423] A mixture of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate (80 mg, 202.8 umol, 1 *eq*), 1-methylpiperazine (40.6 mg, 405.7

umol, 45.0 uL, 2 *eq*), Cs_2CO_3 (132.1 mg, 405.7 umol, 2 *eq*), RuPhos Pd G3 (16.9 mg, 20.2 umol, 0.1 *eq*) in THF (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 12 hr under N_2 atmosphere. LCMS showed desired compund fromed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,9min) to give 5,6-dimethyl-9-(4-methylpiperazin-1-yl)-6H-pyrido[4,3-b]carbazole.

[00424] MS (ESI): *m/z* =345.1 $[M+H]^+$

[00425] **5,6-dimethyl-9-(piperazin-1-yl)-6H-pyrido[4,3-b]carbazole (Compound 244)**



[00426] Step 1: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate

[00427] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (269 mg, 1.0 mmol, 1 *eq*) in THF (7 mL) was added t-BuOK (230.1 mg, 2.0 mmol, 2 *eq*) at 0°C. The mixture was stirred at 0°C for 10 min. And then 1,1,1-trifluoro-N-phenyl-N-((trifluoromethyl)sulfonyl)methanesulfonamide (439.6 mg, 1.2 mmol, 1.2 *eq*) was added to the above mixture. The mixture was stirred at 25°C for 12 hr. LCMS showed desired compound was detected. The reaction mixture was partitioned between H_2O 100 mL and EtOAc (50mL × 3). And the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ethergradient @ 75 mL/min) to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate.

[00428] Step 2: tert-butyl 4-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)piperazine-1-carboxylate

[00429] A mixture of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate (80 mg, 202.8 umol, 1 *eq*), tert-butyl piperazine-1-carboxylate

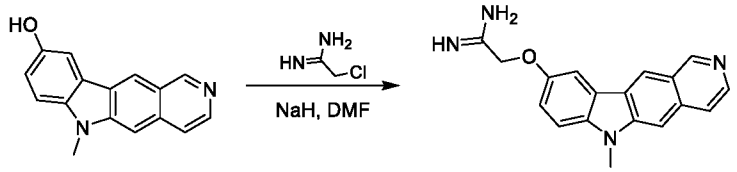
hydrochloride (90.3 mg, 405.7 umol, 2 *eq*), Cs_2CO_3 (132.1 mg, 405.7 umol, 2 *eq*), Ru phos Pd G3 (16.9 mg, 20.2 umol, 0.1 *eq*) in THF (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 C for 12 hr under N_2 atmosphere. LCMS showed desired compund fromed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO2, DCM: MeOH = 10:1) to give tert-butyl 4-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)piperazine-1-carboxylate.

[00430] Step 3: 5,6-dimethyl-9-(piperazin-1-yl)-6H-pyrido[4,3-b]carbazole

[00431] To a solution of tert-butyl 4-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)piperazine-1-carboxylate (71 mg, 164.9 umol, 1 *eq*) in TFA (1 mL) and DCM (2 mL). The mixture was stirred at 25 C for 1 hr. LCMS showed desired compound formed. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-33%,8min) to give 5,6-dimethyl-9-(piperazin-1-yl)-6H-pyrido[4,3-b]carbazole.

[00432] MS (ESI): *m/z* =331.1 $[M+H]^+$

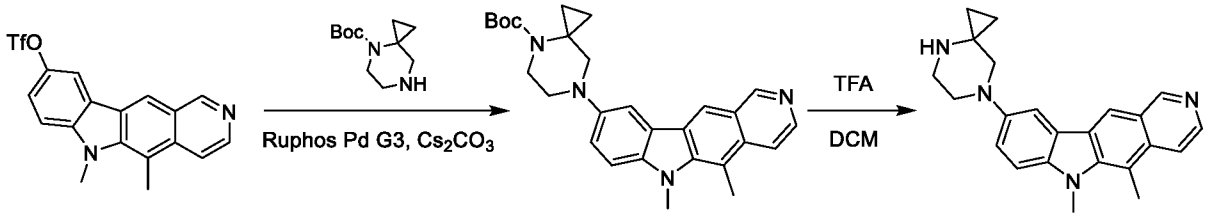
[00433] **2-((6-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)acetimidamide (Compound 245)**



[00434] To a solution of 6-methylpyrido[4,3-b]carbazol-9-ol (100 mg, 402.7 µmol, 1 eq) in DMF (4.0 mL) were added NaH (77.3 mg, 1.93 mmol, 60% purity, 4.8 eq) and 2-chloroacetamidine (77.9 mg, 604.1 µmol, 1.5 eq, HCl). The mixture was stirred at 70°C for 12 hrs. LCMS showed the reaction was completed and desired product was detected. The mixture was poured into NH_4Cl (10 mL) and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition: Phenomenex Luna C18 100*30mm*5µm;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-30%,7min) to afford 2-((6-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy).

[00435] MS (ESI): *m/z* = 305.0 $[M+H]^+$

[00436] **5,6-dimethyl-9-(4,7-diazaspiro[2.5]octan-7-yl)-6H-pyrido[4,3-b]carbazole (Compound 246)**



[00437] Step 1: tert-butyl7-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate

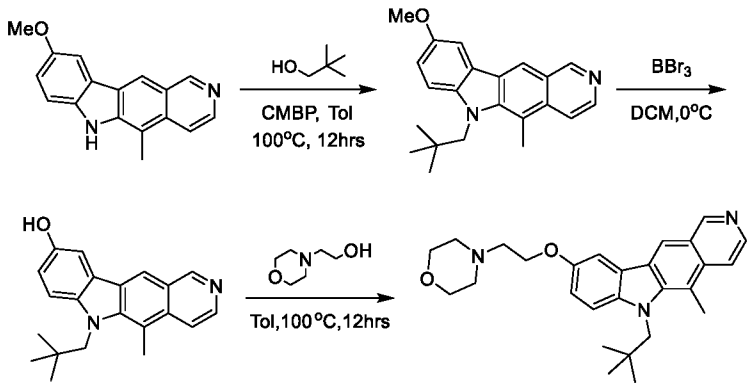
[00438] A mixture of (5,6-dimethylpyrido[4,3-b]carbazol-9-yl) trifluoromethanesulfonate (100 mg, 253.5 umol, 1 eq), tert-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate (161.4 mg, 760.7 umol, 3 eq), Cs_2CO_3 (247.8 mg, 760.7 umol, 3 eq) and RuPhos Pd G3 (42.4 mg, 50.7 umol, 0.2 eq) in THF (4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 12 hr under N_2 atmosphere. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2, Petroleum ether/Ethyl acetate=0/1) to afford tert-butyl 7-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate.

[00439] Step 2; 5,6-dimethyl-9-(4,7-diazaspiro[2.5]octan-7-yl)-6H-pyrido[4,3-b]carbazole

[00440] To a solution of tert-butyl 7-(5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)-4,7-diazaspiro[2.5]octane-4-carboxylate (70 mg, 153.3 umol, 1 eq) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25°C for 0.5 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 80*40mm*3 um; mobile phase: [water(0.1%TFA)-ACN];B%: 3%-27%,7min) to afford 5,6-dimethyl-9-(4,7-diazaspiro[2.5]octan-7-yl)-6H-pyrido[4,3-b]carbazole.

[00441] MS (ESI): *m/z* = 357.1 $[M+H]^+$

[00442] **4-(2-((5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 247)**



[00443] Step 1: 9-methoxy-5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazole

[00444] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (400 mg, 1.5 mmol, 1 eq) in Tol. (2 mL) was added 2,2-dimethylpropan-1-ol (268.8 mg, 3.0 mmol, 328.7 µL, 2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (552.0 mg, 2.2 mmol, 1.5 eq). The mixture was stirred at 100°C for 12 hrs under N_2. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ethergradient @ 70 mL/min) to give 9-methoxy-5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazole.

[00445] Step 2: 5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-ol

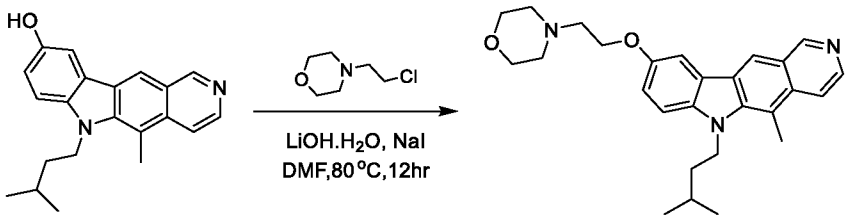
[00446] To a solution of 9-methoxy-5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazole (450 mg, 1.35 mmol, 1 eq) in DCM (10 mL) was added BBr_3 (1.7 g, 6.7 mmol, 652.1 µL, 5 eq). The mixture was stirred at 0°C for 2 hrs. LC-MS showed desired compound was detected. The reaction was poured into saturated aqueous $NaHCO_3$ (30 mL). The aqueous phase was washed with H_2O (10 mL × 3), filtered and concentrated under reduced pressure to give 5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-ol

[00447] Step 3: 4-(2-((5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine

[00448] To a solution of 5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-ol (80 mg, 251.25 µmol, 1 eq) in Tol. (3 mL) was added 2-morpholinoethanol (32.9 mg, 251.2 µmol, 30.8 µL, 1 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (121.2 mg, 502.4 µmol, 2 eq). The mixture was stirred at 100°C for 12 hrs under N_2. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-34%,8min) to give 4-(2-((5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine.

[00449] MS (ESI): *m/z* = 432.2 $[M+H]^+$

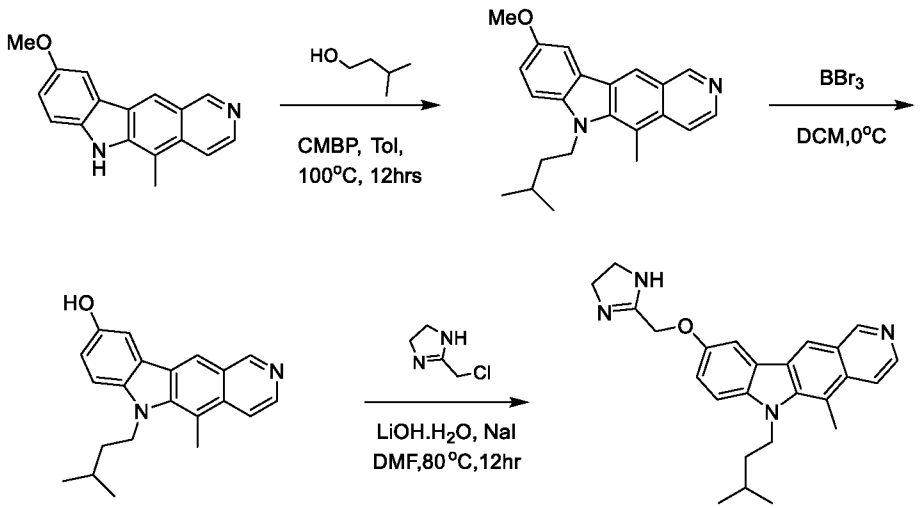
[00450] **4-(2-((6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 248)**



[00451] To a solution of 6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol (80 mg, 251.2 umol, 1 *eq*) in DMF (4 mL) was added 4-(2-chloroethyl)morpholine (111.8 mg, 502.4 umol, 2 *eq*, HCl), $LiOH.H_2O$ (42.1 mg, 1.0 mmol, 4 *eq*) and NaI (37.6 mg, 251.2 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100 * 40 mm * 5 um; mobile phase: [water (0.1% TFA)-ACN]; B%: 5%-38%, 8min) to give 4-[2-(6-isopentyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine.

[00452] MS (ESI): *m/z* = 432.3 $[M+H]^+$

[00453] **9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopentyl-5-methyl-pyrido[4,3-b]carbazole (Compound 249)**



[00454] Step 1: 6-isopentyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00455] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (400 mg, 1.5 mmol, 1 eq) in Tol (2 mL) was added 3-methylbutan-1-ol (134.4 mg, 1.5 mmol, 166.0 uL, 1 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (441.6 mg, 1.83 mmol, 1.2 eq). The mixture was stirred at 100°C for 12 hrs under N_2. LC-MS showed desired compound was

detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ethergradient @ 70mL/min) to give

[00456] 6-isopentyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole.

[00457] Step 2; 6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

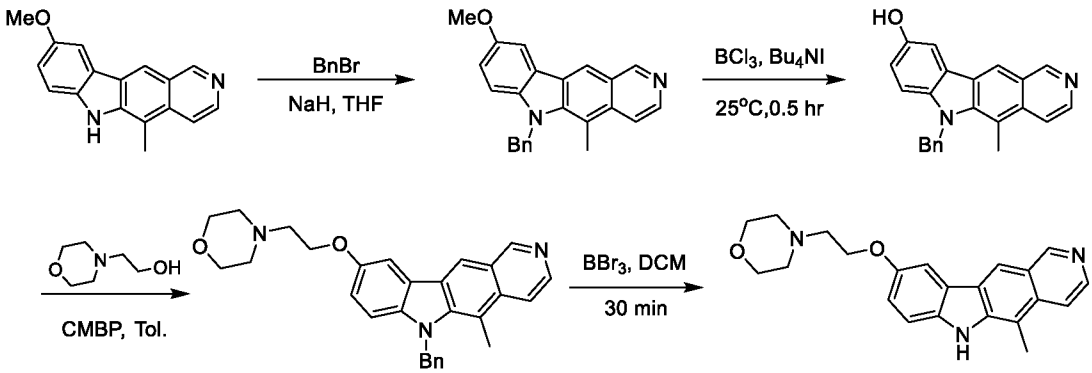
[00458] To a solution of 6-isopentyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole (410 mg, 1.2 mmol, 1 eq) in DCM (8 mL) was added BBr_3 (1.5 g, 6.1 mmol, 594.1 uL, 5 eq). The mixture was stirred at 0°C 2 hrs. LC-MS showed desired compound was detected. The reaction was slowly added to $NH_3.H_2O$ (25% purity, 10 mL) at 0°C. The mixture was filtered and the cake was washed with H_2O (10 mL × 3). The combined aqueous was washed with DCM (10 mL × 3). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give 6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol.

[00459] Step 3; 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazole

[00460] To a solution of 6-isopentyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol (80 mg, 251.2 umol, 1 *eq*) in DMF (4 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (46.7 mg, 301.5 umol, 1.2 *eq*, HCl) and $LiOH.H_2O$ (42.1 mg, 1.0 mmol, 4 *eq*) and NaI (37.6 mg, 251.2 umol, 1 *eq*) was added in the mixture was stirred at 80°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition , column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 5%-38%,8min) to give 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopentyl-5-methyl- pyrido[4,3-b]carbazole.

[00461] MS (ESI): *m/z* = 401.1 $[M+H]^+$

[00462] **4-(2-((5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 250)**



[00463] Step 1: 6-benzyl-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00464] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (500 mg, 1.9 mmol, 1 *eq*) in THF (15 mL) was added NaH (228.7 mg, 5.7 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. Bromomethylbenzene (326.0 mg, 1.9 mmol, 226.4 uL, 1 *eq*) was added to the mixture at 0°C and stirred at 25°C for 12 hr. LCMS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl (50 mL) and EtOAc (50 mL × 3). The organic phase was separated, washed with brine (30mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ethergradient @ 75 mL/min) to give 6-benzyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole.

[00465] Step 2: 6-benzyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

[00466] 6-benzyl-9-methoxy-5-methyl-pyrido[4,3-b]carbazole (90 mg, 255.3 umol, 1 *eq*) and Bu_4NI (188.6 mg, 510.7 umol, 2 *eq*) were added to BCl_3 (5 mL) at 25°C. The mixture was stirred at 25°C for 30 min. LC-MS showed the desired compound was detected. The reaction mixture was added to $NaHCO_3$ (10 mL) and filtered and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give 6-benzyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-ol.

[00467] Step 3: 4-(2-((6-benzyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine

[00468] To a solution of 6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-ol (100 mg, 295.5 umol, 1 *eq*) in Tol. (4 mL) was added 2-morpholinoethanol (46.5 mg, 354.6 umol, 43.4 uL, 1.2 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (142.6 mg, 591.0 umol, 2 *eq*) under N_2. The mixture was stirred at 100°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH =10:1) to give 4-[2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine.

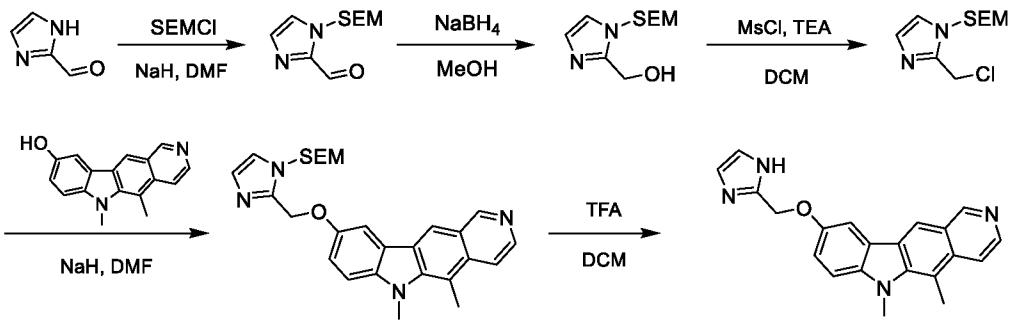
[00469] Step 4: 4-(2-((5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine

[00470] To a solution of 4-[2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine (30 mg, 66.4 umol, 1 *eq*) in DCM (1 mL) was added BBr_3 (83.2 mg, 332.1 umol, 32.0 uL, 5 *eq*) at -20°C. The mixture was stirred at -20°C for 30 min. LC-MS showed the desired compound was detected. The reaction was added to $NH_3.H_2O$ (5 mL). The reaction mixture was partitioned between H_2O 5 mL and CH_2Cl_2 (5 mL × 3). The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced

pressure to give a residue. The residue was purified by prep-HPLC (TFA condition column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-25%,8min) to give 4-(2-((5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine.

[00471] MS (ESI): *m/z* = 362.1 $[M+H]^+$

[00472] **9-((1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 251)**



[00473] Step 1: 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-2-carbaldehyde

[00474] To a solution of 1H-imidazole-2-carbaldehyde (1.0 g, 10.4 mmol, 1 eq) in DMF (30 mL) was added NaH (499.5 mg, 12.4 mmol, 60% purity, 1.2 eq) at 25°C. After 1.5 hr, SEM-Cl (1.9 g, 11.4 mmol, 2.0 mL, 1.1 eq) was added to the above mixture and the mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completely. The reaction was quenched with saturated NH_4Cl (15 mL) and extracted with ethyl acetate (30 mL × 3). The combined organic phase was washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=0/1 to 3/1) to afford 1-(2-trimethylsilylethoxymethyl)imidazole-2-carbaldehyde.

[00475] Step 2: (1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol

[00476] To a solution of 1-(2-trimethylsilylethoxymethyl)imidazole-2-carbaldehyde (1.0 g, 4.4 mmol, 1 eq) in MeOH (15 mL) was added $NaBH_4$ (200.5 mg, 5.3 mmol, 1.2 eq) at -20°C. The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to remove MeOH, and then dissolved in ethyl aetate (25 mL), poured into saturated aqueous $NaHCO_3$ (15 mL) and then separated. The organic phase was washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ethergradient @ 50 mL/min) to give (1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methanol.

[00477] Step 3: 2-(chloromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole

[00478] To a solution of [1-(2-trimethylsilylethoxymethyl)imidazol-2-yl]methanol (500 mg, 2.1 mmol, 1 *eq*) in DCM (20 mL) was added TEA (664.6 mg, 6.5 mmol, 914.2 uL, 3 *eq*) and methanesulfonyl chloride (400.0 mg, 3.4 mmol, 270.2 uL, 1.5 *eq*). The mixture was stirred at 25°C for 2.5 hr. LCMS showed desired compound formed. The reaction was quenched with saturated H_2O (15 mL) and extracted with DCM (30 mL×3), dried over anhydrous Na_2SO_4, filtered and concentrated to give 2-[[2-(chloromethyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane.

[00479] Step 4: 5,6-dimethyl-9-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

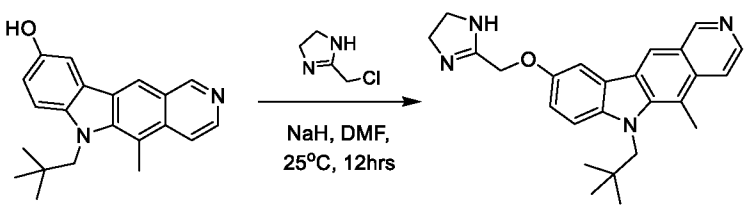
[00480] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 *eq*) in DMF (2 mL) was added NaH (45.7 mg, 1.1 mmol, 60% purity, 3 *eq*) at 0°C and the mixture was stirred for 0.5 hr. 2-[[2-(chloromethyl)imidazol-1-yl]methoxy]ethyl-trimethyl-silane (103.5 mg, 419.3 umol, 10.7 uL, 1.1 *eq*) and NaI (57.1 mg, 381.2 umol, 1 *eq*) was added to the above mixture. The mixture was stirred at 25°C for 12 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO2, DCM: MeOH = 10:1) to afford 5,6-dimethyl-9-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

[00481] Step 5: 9-((1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00482] To a solution of 5,6-dimethyl-9-((1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole (60 mg, 126.9 umol, 1 *eq*) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25°C for 0.5 hr. LCMS showed the reaction was completely. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-35%,7min) to afford 9-((1H-imidazol-2-yl)methoxy)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00483] MS (ESI): *m/z* = 343.0 $[M+H]^+$

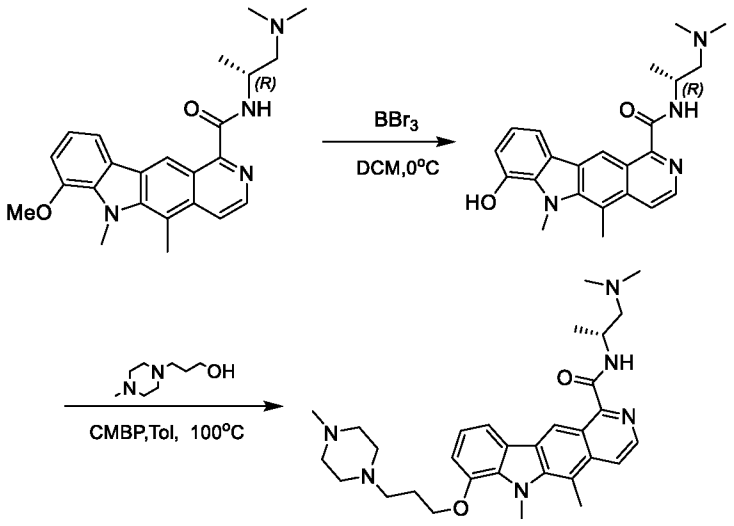
[00484] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazole (Compound 252)**



[00485] To a solution of 5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazol-9-ol (25 mg, 78.5 umol, 1 eq) in DMF (3 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (11.1 mg, 94.2 umol, 1.2 eq), NaH (12.5 mg, 314.0 umol, 60% purity, 4 eq) was added in the mixture was stirred at 25°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 13%-30%,8min) to give 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6-neopentyl-6H-pyrido[4,3-b]carbazole.

[00486] MS (ESI): *m/z* = 401.1[M+H]$^+$

[00487] **(R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-7- (3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 253)**



[00488] Step 1: (R)-N-(1-(dimethylamino)propan-2-yl)-7-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

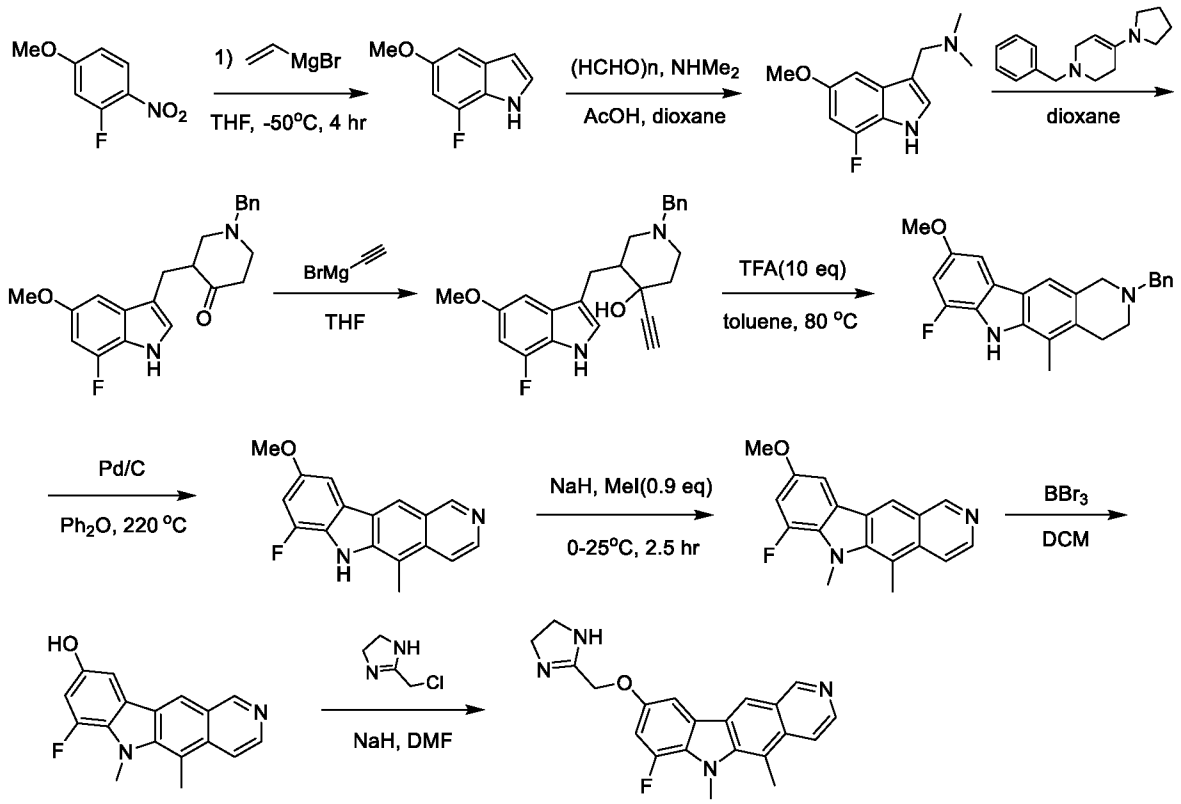
[00489] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-7-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (30 mg, 74.1 umol, 1 eq) in DCM (3 mL) was added BBr_3 (92.9 mg, 370.8 umol, 35.7 uL, 5 eq). The mixture was stirred at 0°C 2 hrs. LC-MS showed desired product was detected. The reaction mixture was quenched by addition $NH_3.H_2O$ 10 mL at 0°C, and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (15 mL × 1), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give (R)-N-(1-(dimethylamino)propan-2-yl)-7-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b] carbazole-1-carboxamide.

[00490] Step 2: (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-7-(3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00491] To a solution of (R)-N-(1-(dimethylamino)propan-2-yl)-7-hydroxy-5,6-dimethyl-6H- pyrido[4,3-b]carbazole-1-carboxamide (25 mg, 64.0 umol, 1 eq) in Tol. (4 mL) was added 3-(4-methylpiperazin-1-yl)propan-1-ol (12.1 mg, 76.8 umol, 1.2 eq) and 2-(tributyl-λ5-phosphanylidene)acetonitrile (46.3 mg, 192.0 umol, 3 eq). The mixture was stirred at 100°C for 12 hrs. LC-MS showed desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition; column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 20%-65%,8min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-7- (3-(4-methylpiperazin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00492] MS (ESI): *m/z* = 531.3 $[M+H]^+$

[00493] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (Compound 254)**



[00494] Step 1: 7-fluoro-5-methoxy-1H-indole

[00495] To a solution of 2-fluoro-4-methoxy-1-nitro-benzene (30 g, 175.3 mmol, 1 *eq*) in THF (600 mL) was added dropwise bromo(vinyl)magnesium (1 M, 876.5 mL, 5 *eq*) at -50°C over 2 hr. Then the mixture was stirred at -50°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl 800 mL and EtOAc 1000 mL. The water phase was separated, extracted with EtOAc (1000 mL × 3).

The combined organic phase was washed with brine (1000 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ethergradient @ 150/min) to give 7-fluoro-5-methoxy-1H-indole.

[00496] Step 2: 1-(7-fluoro-5-methoxy-1H-indol-3-yl)-N,N-dimethylmethanamine

[00497] To a solution of 7-fluoro-5-methoxy-1H-indole (4.2 g, 25.43 mmol, 1 *eq*) in dioxane (40 mL) and H_2O (40 mL) was added N-methylmethanamine;hydrochloride (2.2 g, 27.9 mmol, 1.1 *eq*), formaldehyde (2.2 g, 27.9 mmol, 2.0 mL, 37% purity, 1.1 *eq*), TEA (2.8 g, 27.9 mmol, 3.8 mL, 1.1 *eq*) and AcOH (2.2 g, 38.1 mmol, 2.1 mL, 1.5 *eq*). The mixture was stirred at 30°C for 12 hr. LC-MS showed the desired compound was detected. The mixture was poured into ice NaOH (400 mL, 2N) and white solid was separate out. The mixture was filtered and washed with H_2O (200 mL) and the cake was collected to give 1-(7-fluoro-5-methoxy-1H-indol-3-yl)-N,N-dimethyl-methanamine.

[00498] Step 3: benzyl-3-((7-fluoro-5-methoxy-1H-indol-3-yl)methyl)piperidin-4-one

[00499] To a solution of 1-(7-fluoro-5-methoxy-1H-indol-3-yl)-N,N-dimethyl-methanamine (4 g, 18.0 mmol, 1 *eq*) in dioxane (55 mL) was added 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine (10.9 g, 44.9 mmol, 2.5 *eq*). The mixture was stirred at 120°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl acetate / Petroleum ethergradient @ 150 mL/min) to give 1-benzyl-3-[(7-fluoro-5-methoxy-1H-indol-3-yl)methyl]piperidin-4-one.

[00500] Step 4: 1-benzyl-4-ethynyl-3-((7-fluoro-5-methoxy-1H-indol-3-yl)methyl)piperidin-4-ol

[00501] To a solution of 1-benzyl-3-[(7-fluoro-5-methoxy-1H-indol-3-yl)methyl]piperidin-4-one (7.6 g, 20.8 mmol, 1 *eq*) in THF (150 mL) was added bromo(ethynyl)magnesium (0.5 M, 167.0 mL, 4 *eq*) at 0 C. The mixture was stirred at 0°C for 1 hr. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl 300 mL and EtOAc 300 mL. The water phase was separated, extracted with EtOAc (300 mL × 3). The combined organic phase was washed with brine (200 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-benzyl-4-ethynyl-3-[(7-fluoro-5-methoxy-1H-indol-3-yl)methyl]piperidin-4-ol.

[00502] Step 5: 2-benzyl-7-fluoro-9-methoxy-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00503] To a solution of 1-benzyl-4-ethynyl-3-[(7-fluoro-5-methoxy-1H-indol-3-yl)methyl]piperidin-4-ol (6.8 g, 17.4 mmol, 1 *eq*) in Tol. (120 mL) was added TFA (19.9 g, 174.7 mmol, 12.9 mL, 10 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The mixture was concentrated to get crude residue and diluted with EtOAc 100 mL and adjusted pH=8 with sat $NaHCO_3$, extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 150 mL/min) to give 2-benzyl-7-fluoro-9-methoxy-5-methyl-1,3,4,6-tetrahydropyrido[4,3-b]carbazole.

[00504] Step 6: 7-fluoro-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole

[00505] To a solution of Pd/C (800 mg, 10% purity) in Ph_2O (7 mL) was added 2-benzyl-7-fluoro-9-methoxy-5-methyl-1,3,4,6-tetrahydropyrido[4,3-b]carbazole (500 mg, 1.3 mmol, 1 *eq*). The mixture was stirred at 220°C for 1 hr under N_2. LC-MS showed the desired compound was detected. The reaction mixture was filtered and the filtrate dried in vacuum to give crude product. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~10% CH_2Cl_2/MeOH@ 150 mL/min) to give 7-fluoro-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole.

[00506] Step 7: 7-fluoro-9-methoxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00507] To a solution of 7-fluoro-9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (480 mg, 1.7 mmol, 1 *eq*) in THF (8 mL) was added NaH (205.4 mg, 5.1 mmol, 60% purity, 3 *eq*) at 0°C and stirred at 0°C for 30 min, and MeI (230.9 mg, 1.6 mmol, 101.2 uL, 0.9 *eq*) was added to the mixture at 0°C. The mixture was stirred at 25°C for 2 hr. TLC indicated Reactant was consumed completely and one major new spot with larger polarity was detected. The reaction mixture was partitioned between NH_4Cl 30 mL and EtOAc 50 mL. The water phase was separated, extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine (20 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue to give 7-fluoro-9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole.

[00508] Step 8: 7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol

[00509] To a solution of 7-fluoro-9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole (500 mg, 1.7 mmol, 1 *eq*) in DCM (20 mL) was added BBr_3 (851.1 mg, 3.4 mmol, 327.3 uL, 2 *eq*)

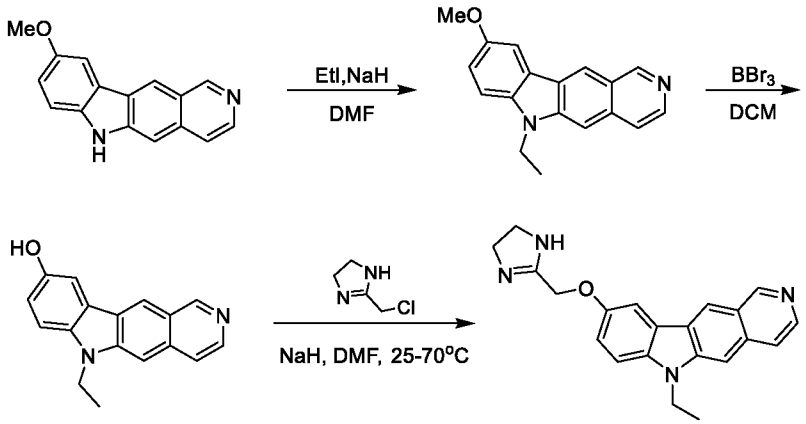
at 0°C. The mixture was stirred at 0°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was added to $NH_3.H_2O$ (purity 25%, 10 mL) and filtered and the filter cake was washed with 20 mL of H_2O, dried in vacuum to give crude product to give 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol.

[00510] Step 9: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00511] To a solution of 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol (40 mg, 142.7 umol, 1 *eq*) in DMF (2 mL) were added NaH (57.0 mg, 1.4 mmol, 60% purity, 10 *eq*) and 2-(chloromethyl)-4,5-dihydro-1H-imidazole (33.8 mg, 285.4 umol, 2 *eq*). The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was quenched by addition HCOOH 1 mL at 25°C and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-20%,9min) to give 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazole.

[00512] MS (ESI): *m/z* = 363.1$[M+H]^+$

[00513] **9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-ethyl-pyrido[4,3-b]carbazole (Compound 255)**



[00514] Step 1: 6-ethyl-9-methoxy-pyrido[4,3-b]carbazole

[00515] To a solution of 9-methoxy-6H-pyrido[4,3-b]carbazole (50 mg, 201.3 umol, 1 *eq*) in DMF (2 mL) was added NaH (16.1 mg, 402.8 umol, 60% purity, 2 *eq*) and the mixture was stirred at 0°C for 30 min. EtI (37.7 mg, 241.7 umol, 19.3 uL, 1.2 *eq*) was added to the mixture and stirred at 25°C for 2 hr. LC-MS showed the desired compound was detected. The mixture was added to the NH_4Cl (20 mL). The residue was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with birne (60 mL × 1), dried over

Na_2SO_4, filtered and concentrated under reduced pressure to give 6-ethyl-9-methoxy-pyrido[4,3-b]carbazole.

[00516] Step 2: 6-ethylpyrido[4,3-b]carbazol-9-ol

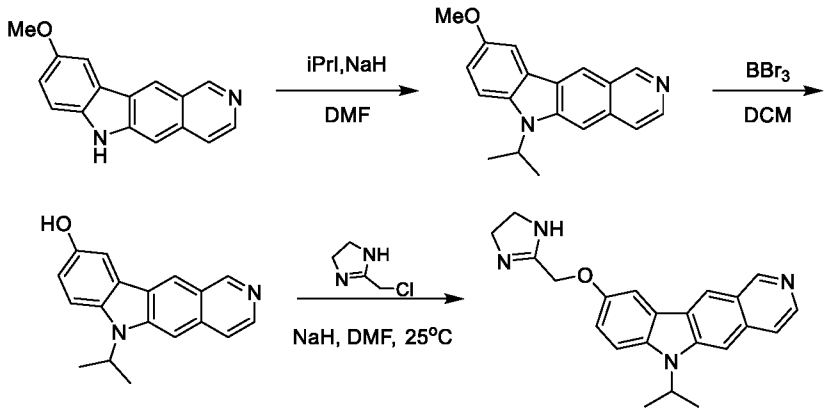
[00517] To a solution of 6-ethyl-9-methoxy-pyrido[4,3-b]carbazole (190 mg, 687.6 umol, 1 eq) in DCM (3 mL) was added BBr_3 (861.3 mg, 3.4 mmol, 331.3 uL, 5 *eq*) at 0°C. The mixture was stirred at 25°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was added to the $NH_3.H_2O$ (40 mL, 25%) at 0°C. The mixture was filtered and the filter cake was washed with 30 mL of H_2O, concentrated under reduced pressure to give 6-ethylpyrido[4,3-b]carbazol-9-ol.

[00518] Step 3: 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-ethyl-pyrido[4,3-b]carbazole

[00519] To a solution of 6-ethylpyrido[4,3-b]carbazol-9-ol (40 mg, 152.5 umol, 1 *eq*) in DMF (3 mL) was added NaH (24.4 mg, 609.9 umol, 60% purity, 4 *eq*) at 25°C and stirred for 30 min. 2-(chloromethyl)-4,5-dihydro-1H-imidazole (28.4 mg, 183.0 umol, 1.2 *eq*, HCl) and NaI (22.9 mg, 152.5 umol, 1 *eq*) was added to the mixture and stirred at 70°C for 1 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition,column: Phenomenex luna C18 100×40mm×5 um;mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-30%,8min) to give 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-ethyl-pyrido[4,3-b]carbazole.

[00520] MS (ESI): *m/z* = 345.1$[M+H]^+$

[00521] **9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopropyl-pyrido[4,3-b]carbazole (Compound 256)**



[00522] Step 1: 6-isopropyl-9-methoxy-6H-pyrido[4,3-b]carbazole

[00523] To a solution of 9-methoxy-6H-pyrido[4,3-b]carbazole (150 mg, 604.1 umol, 1 *eq*) in DMF (6 mL) was added NaH (72.4 mg, 1.8 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. 2-iodopropane (308.1 mg, 1.8 mmol, 181.2 uL, 3 *eq*) was added to the mixture and stirred for 2 hr at 65°C. LC-MS showed the desired compound was detected. The reaction mixture was partitioned between NH_4Cl 20 mL and EtOAc 50 mL. The water phase was separated, extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine (30 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 6-isopropyl-9-methoxy-pyrido[4,3-b]carbazole.

[00524] Step 2: 6-isopropyl-6H-pyrido[4,3-b]carbazol-9-ol

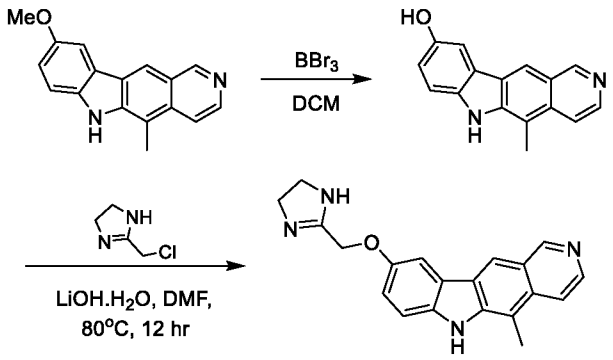
[00525] To a solution of 6-isopropyl-9-methoxy-pyrido[4,3-b]carbazole (300 mg, 1.0 mmol, 1 *eq*) in DCM (5 mL) was added BBr_3 (1.2 g, 5.1 mmol, 497.7 uL, 5 *eq*) at 0°C. The mixture was stirred at 25°C for 1 hr. LC-MS showed the desired compound was detected. The reaction mixture was added to $NH_3.H_2O$ (purity 25%, 8 mL), filtered and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give 6-isopropylpyrido[4,3-b]carbazol-9-ol.

[00526] Step 3: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-isopropyl-6H-pyrido[4,3-b]carbazole

[00527] To a solution of 6-isopropylpyrido[4,3-b]carbazol-9-ol (60 mg, 217.13 umol, 1 *eq*) in DMF (3 mL) was added NaH (26.0 mg, 651.3 umol, 60% purity, 3 *eq*) at 25°C and stirred for 30 min, 2-(chloromethyl)-4,5-dihydro-1H-imidazole (40.3 mg, 260.5 umol, 1.2 *eq*, HCl) and NaI (32.5 mg, 217.1 umol, 1 *eq*) was added to the mixture. The mixture was stirred at 25°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,9min) to give 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-6-isopropyl-pyrido[4,3-b]carbazole.

[00528] MS (ESI): *m/z* = 359.1$[M+H]^+$

[00529] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6H-pyrido[4,3-b]carbazole (Compound 257)**



[00530] Step 1: 5-methyl-6H-pyrido[4,3-b]carbazol-9-ol

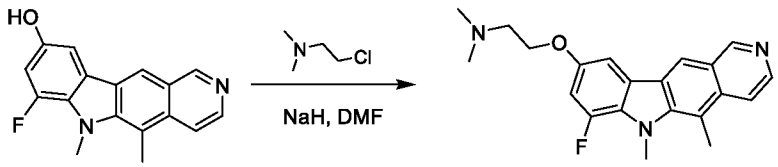
[00531] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (100 mg, 381.2 umol, 1 *eq*) in DCM (2 mL) was added BBr_3 (477.5 mg, 1.9 mmol, 183.6 uL, 5 *eq*) at 0°C. The mixture was stirred at 25°C for 1 hr. LC-MS showed the desired compound was detected. The reaction mixture was added to $NH_3.H_2O$ (purity 25%, 4 mL) and filtered and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give 5-methyl-6H-pyrido[4,3-b]carbazol-9-ol.

[00532] Step 2: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-5-methyl-6H-pyrido[4,3-b]carbazole

[00533] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazol-9-ol (60 mg, 241.6 umol, 1 *eq*) in DMF (3 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole (44.9 mg, 290.0 umol, 1.2 *eq*, HCl), $LiOH.H_2O$ (30.4 mg, 724.9 umol, 3 *eq*) and NaI (36.2 mg, 241.6 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-36%,8min) to give 9-(4,5-dihydro-1H-imidazol-2-ylmethoxy)-5-methyl-6H-pyrido[4,3-b]carbazole.

[00534] MS (ESI): *m/z* = 331.1M+H]$^+$

[00535] **2-((7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N,N-dimethylethanamine (Compound 258)**

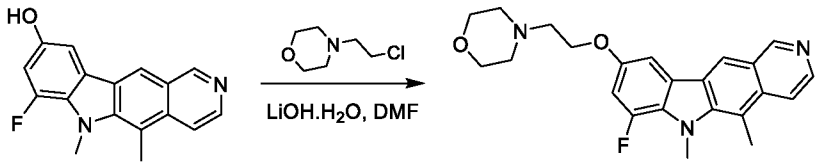


[00536] To a solution of 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol (80 mg, 285.4 umol, 1 *eq*) in DMF (3 mL) was added NaH (34.2 mg, 856.2 umol, 60% purity, 3 *eq*) 2-chloro-N,N-dimethyl-ethanamine (49.3 mg, 342.5 umol, 1.2 *eq*, HCl) the mixture was atirred

at 25°C for 30 min, 2-chloro-N,N-dimethyl-ethanamine (49.3 mg, 342.5 umol, 1.2 *eq*, HCl) was added to the mixture. The mixture was stirred at 70°C for 2 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-30%,8min) to give 2-(7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-yl)oxy-N,N-dimethyl-ethanamine.

[00537] MS (ESI): *m/z* = 352.1[M+H]$^+$

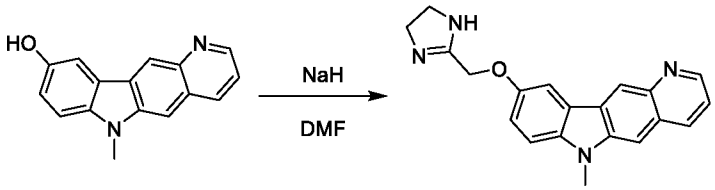
[00538] **4-(2-((7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)morpholine (Compound 259)**



[00539] To a solution of 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol (80 mg, 285.4 umol, 1 *eq*) in DMF (2 mL) was added 4-(2-chloroethyl)morpholine (63.7 mg, 342.5 umol, 1.2 *eq*, HCl), $LiOH.H_2O$ (35.9 mg, 856.2 umol, 3 *eq*) and NaI (42.7 mg, 285.4 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. LC-MS showed the desired compound was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-30%,8min) to give 4-[2-(7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]morpholine.

[00540] MS (ESI): *m/z* = 394.2[M+H]$^+$

[00541] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-methyl-6H-pyrido[3,2-b]carbazole (Compound 260)**

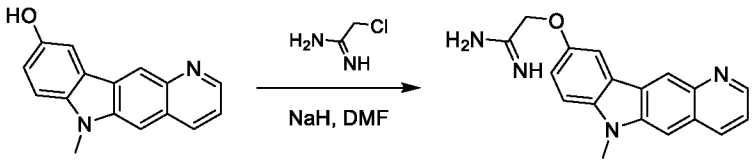


[00542] To a solution of 6-methyl-6H-pyrido[3,2-b]carbazol-9-ol (40 mg, 161.1 umol, 1 eq) in DMF (2 mL) were added NaH (64.4 mg, 1.6 mmol, 60% purity, 10 eq) and 2-(chloromethyl)-4,5-dihydro-1H-imidazole (49.9 mg, 322.2 umol, 2 eq, HCl). The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was quenched by addition HCOOH (1 mL) at 25°C and

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-25%,8min) to give 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6-methyl-6H-pyrido[3,2-b]carbazole.

[00543] MS (ESI): *m/z* = 331.0 $[M+H]^+$

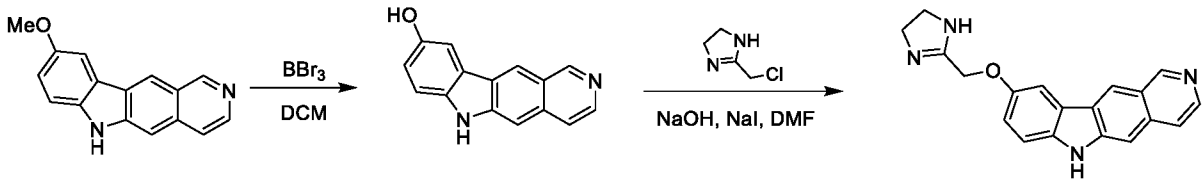
[00544] **2-((6-methyl-6H-pyrido[3,2-b]carbazol-9-yl)oxy)acetimidamide (Compound 261)**



[00545] To a solution of 6-methylpyrido[3,2-b]carbazol-9-ol (46 mg, 185.2 umol, 1 eq) in DMF (2 mL) were added NaH (74.1 mg, 1.8 mmol, 60% purity, 10 eq) and 2-chloroacetamidine (47.8 mg, 370.5 umol, 2 eq, HCl). The mixture was stirred at 25°C for 1 hr. LCMS showed the reaction was completed and desired product was detected. The reaction mixture was quenched by addition HCOOH (1 mL) at 25°C and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-25%,8min) to afford 2-(6-methylpyrido[3,2-b]carbazol-9-yl)oxyacetamidine.

[00546] MS (ESI): *m/z* = 305.1 $[M+H]^+$

[00547] **9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole (Compound 262)**



[00548] Step 1: 6H-pyrido[4,3-b]carbazol-9-ol

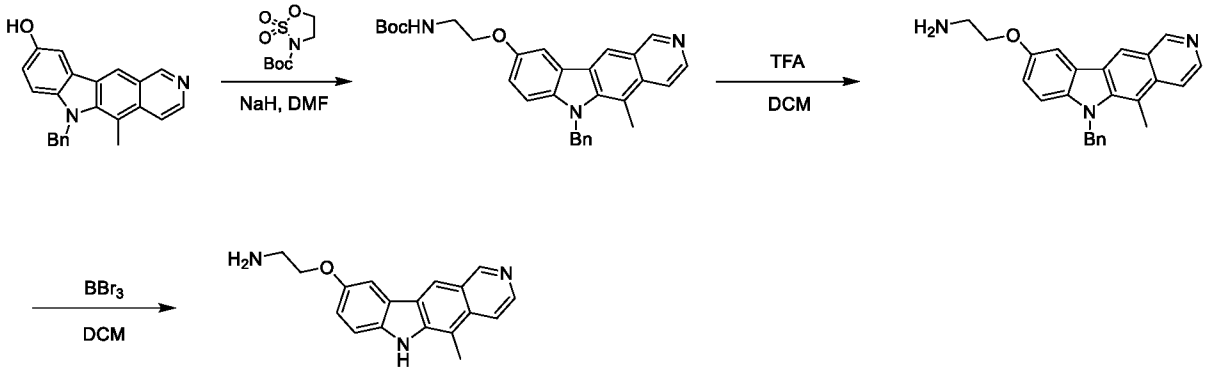
[00549] To a solution of 9-methoxy-6H-pyrido[4,3-b]carbazole (400 mg, 1.6 mmol, 1 eq) in DCM (15 mL) was added BBr_3 (2.0 g, 8.0 mmol, 776.1 uL, 5 eq) at 0°C. The mixture was stirred at 25°C for 2 hr. LCMS showed the reaction was completely. The reaction was slowly added to $NH_3.H_2O$ (25% purity, 30 mL) at 0°C. The mixture was filtered, and the collected solid was washed with H_2O (20 mL × 3). The combined aqueous was extracted with DCM (20 mL × 3). The collected solid and the organic extracts were combined and dried over anhydrous Na_2SO_4 and concentrated to give 6H-pyrido[4,3-b]carbazol-9-ol.

[00550] Step 2: 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole

[00551] To a solution of 6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 213.4 umol, 1 eq) in DMF (2 mL) was added 2-(chloromethyl)-4,5-dihydro-1H-imidazole;hydrochloride (39.7 mg, 256.1 umol, 1.2 eq), NaOH (25.6 mg, 640.3 umol, 3 eq) and sodium iodide (31.9 mg, 213.4 umol, 1 eq). The mixture was stirred at 70°C for 12 hr. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Gemini-NX 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN];B%: 1%-23%,9min) to afford 9-((4,5-dihydro-1H-imidazol-2-yl)methoxy)-6H-pyrido[4,3-b]carbazole.

[00552] MS (ESI): *m/z* = 317.1 $[M+H]^+$

[00553] **2-[(5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy]ethanamine (Compound 263)**



[00554] Step 1: tert-butyl (2-((6-benzyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)carbamate

[00555] To a solution of 6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-ol (60 mg, 177.3 umol, 1 *eq*) in DMF (5 mL) was added NaH (21.2 mg, 531.9 umol, 60% purity, 3 *eq*) and the solution was stirred at 25°C for 30 min. Tert-butyl 2,2-dioxooxathiazolidine-3-carboxylate (47.5 mg, 212.7 umol, 1.2 *eq*) was added to the mixture and stirred at 70°C for 12 hr. The reaction mixture was partitioned between NH_4Cl 5 mL and EtOAc 5 mL. The water phase was separated, extracted with EtOAc (5 mL × 3). The combined organic phase was washed with brine (5 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl N-[2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]carbamate.

[00556] Step 2: 2-((6-benzyl-5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine

[00557] To a solution of tert-butyl N-[2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethyl]carbamate (50 mg, 103.8 umol, 1 *eq*) in DCM (5 mL) was added TFA (35.5 mg, 311.4 umol, 23.0 uL, 3 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture

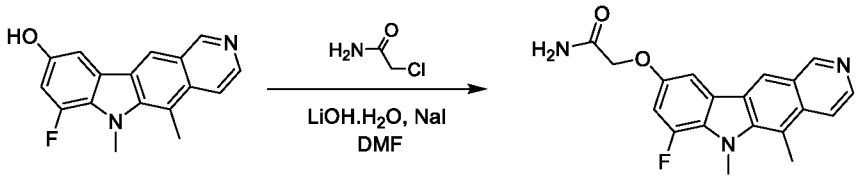
was concentrated under reduced pressure to give 2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethanamine.

[00558] Step 3: 2-((5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethanamine

[00559] To a solution of 2-(6-benzyl-5-methyl-pyrido[4,3-b]carbazol-9-yl)oxyethanamine (50 mg, 131.0 umol, 1 *eq*) in DCM (3 mL) was added BBr_3 (164.1 mg, 655.3 umol, 63.1 uL, 5 *eq*) at -20°C. The mixture was stirred at -20°C for 30 min. The reaction mixture was added to ice $NH_3.H_2O$ (purity 25%, 4 mL) and filtered. The collected solid was washed with 5 mL of H_2O and dried in vacuum to give a residue. The residue was purified by prep-HPLC (TFA condition, column: 3_Phenomenex Luna C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,10min) to give 2-[(5-methyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy]ethanamine.

[00560] MS (ESI): *m/z* = 292.1 $[M+H]^+$

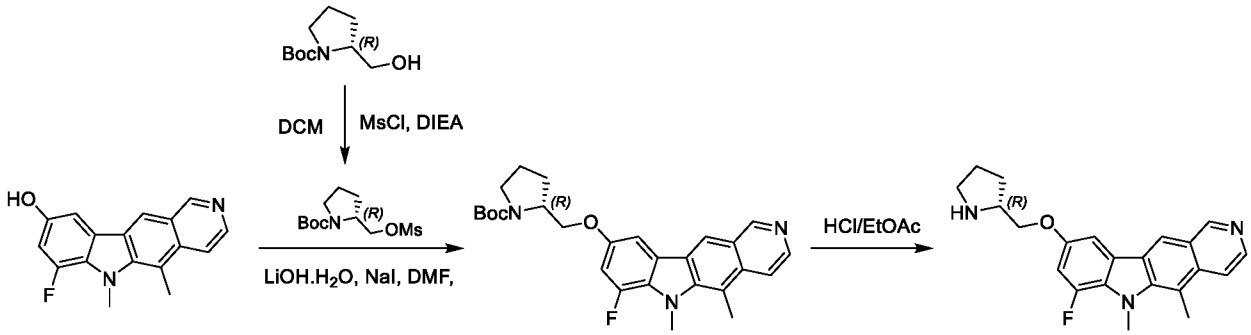
[00561] **2-(7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-yl)oxyacetamide (Compound 264)**



[00562] To a solution of 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol (30 mg, 107.0 umol, 1 *eq*) in DMF (2 mL) was added 2-chloroacetamide (12.0 mg, 128.4 umol, 1.2 *eq*), $LiOH.H_2O$ (17.9 mg, 428.1 umol, 4 *eq*) and NaI (16.0 mg, 107.0 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 5%-30%,8min) to give 2-(7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-yl)oxyacetamide.

[00563] MS (ESI): *m/z* = 338.1 $[M+H]^+$

[00564] **(R)-7-fluoro-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole (Compound 265)**



[00565] Step 1: (R)-tert-butyl 2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate

[00566] To a solution of tert-butyl (2R)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (100 mg, 496.8 umol, 1 *eq*) in DCM (3 mL) was added DIEA (192.6 mg, 1.4 mmol, 259.6 uL, 3 *eq*) and MsCl (113.8 mg, 993.7 umol, 76.9 uL, 2 *eq*) at 0°C. The mixture was stirred at 25°C for 1 hr. The reaction mixture diluted with $NaHCO_3$ 5 mL and extracted with DCM (5 mL × 2). The combined organic layers were washed with brine (10 mL ×1), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give tert-butyl (R)-tert-butyl 2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate.

[00567] Step 2: (R)-tert-butyl 2-(((7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate

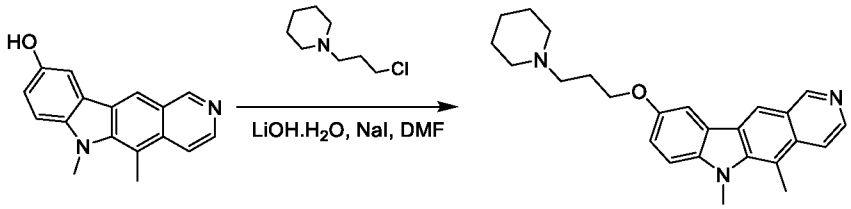
[00568] To a solution of 7-fluoro-5,6-dimethyl-pyrido[4,3-b]carbazol-9-ol (45 mg, 160.5 umol, 1 *eq*) in DMF (2 mL) was added (R)-tert-butyl 2-(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate (42.3 mg, 192.6 umol, 1.2 *eq*), $LiOH.H_2O$ (26.9 mg, 642.1 umol, 4 *eq*) and NaI (24.0 mg, 160.5 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was partitioned between H_2O 5 mL and EtOAc 10 mL. The water phase was separated, extracted with EtOAc (10 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (R)-tert-butyl 2-(((7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate.

[00569] Step 3: (R)-7-fluoro-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole

[00570] A mixture of (R)-tert-butyl 2-(((7-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)methyl)pyrrolidine-1-carboxylate (100 mg, 215.7 umol, 1 *eq*) in HCl / EtOAc (2 mL) (4 N) was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (HCl condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase:[water(0.05%HCl)-ACN];B%: 1%-25%,8min) to give (R)-7-fluoro-5,6-dimethyl-9-(pyrrolidin-2-ylmethoxy)-6H-pyrido[4,3-b]carbazole.

[00571] MS (ESI): *m/z* = 364.1 $[M+H]^+$

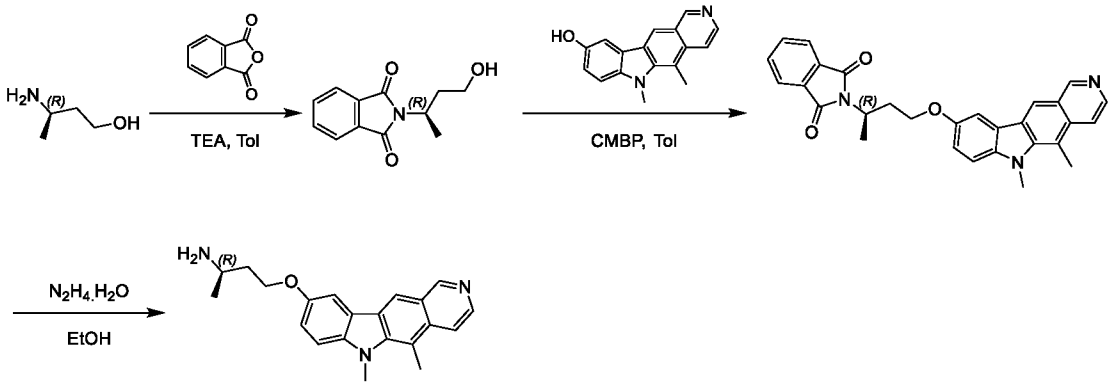
[00572] **5,6-dimethyl-9-(3-(piperidin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole (Compound 266)**



[00573] To a solution of 1-(3-chloropropyl)piperidine (30.2 mg, 152.4 umol, 1.0 eq, HCl) in DMF (2 mL) was added 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (40 mg, 152.4 umol, 1 eq), $LiOH.H_2O$ (25.5 mg, 609.9 umol, 4 eq) and NaI (22.8 mg, 152.4 umol, 1 eq). The mixture was stirred at 80°C for 12 hr. The reaction was concentrated, and the residue was purified by prep-HPLC (HCl condition; column: Welch Xtimate C18 100*25mm*3um;mobile phase: [water(0.05%HCl)-MeOH];B%: 25%-55%,8min) to afford 5,6-dimethyl-9-(3-(piperidin-1-yl)propoxy)-6H-pyrido[4,3-b]carbazole.

[00574] MS (ESI): *m/z* = 388.1 $[M+H]^+$

[00575] **(R)-4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine (Compound 267)**



[00576] Step 1: (R)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione

[00577] To a solution of (R)-3-aminobutan-1-ol (1.6 g, 11.2 mmol, 1 *eq*) in Tol (10 mL) was added (3R)-3-aminobutan-1-ol (1 g, 11.2 mmol, 1 *eq*) and TEA (385.9 mg, 3.8 mmol, 530.9 uL, 0.3 *eq*). The mixture was stirred at 110°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% Petroleum ether gradient / Ethyl acetate @ 80 mL/min) to give (R)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione.

[00578] Step 2: (R)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione

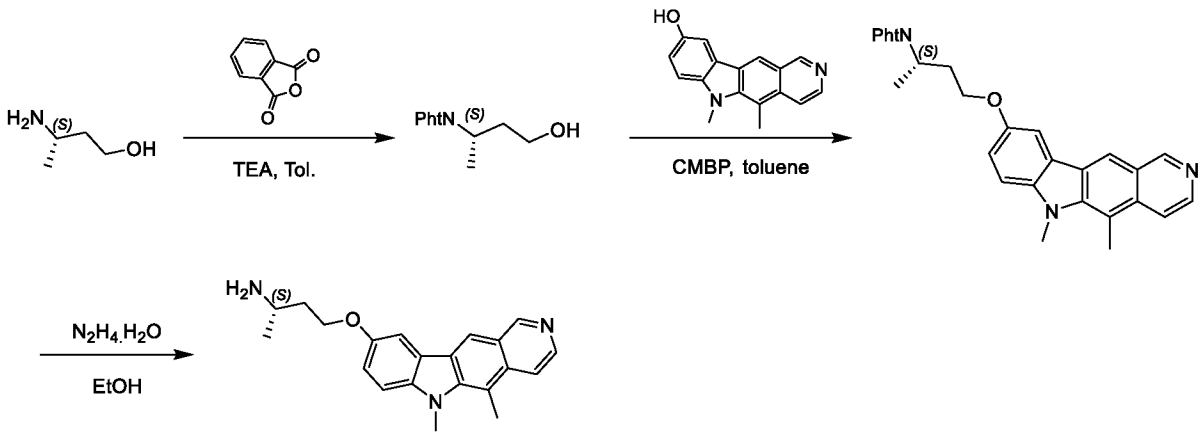
[00579] To a solution of (R)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione (49.8 mg, 190.0 umol, 1 *eq*) in Tol (3 mL) was added 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (50 mg, 228.0 umol, 1.2 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (229.3 mg, 950.2 umol, 5 *eq*) under N_2. The mixture was stirred at 100°C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove **solvent**. The residue was purified by prep-TLC (SiO_2, **DCM / MeOH = 10 / 1**) to give (R)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione.

[00580] Step 3: (R)-4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine

[00581] To a solution of (R)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione (30 mg, 64.7 umol, 1 *eq*) in EtOH (2 mL) was added $N_2H_4.H_2O$ (66.1 mg, 1.2 mmol, 64.2 uL, 98% purity, 20 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL × 2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,10min) to give (R)-4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine.

[00582] MS (ESI): *m/z* = 334.1 $[M+H]^+$

[00583] **((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine (Compound 268)**



[00584] Step 1: (S)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione

[00585] To a solution of isobenzofuran-1,3-dione (1.6 g, 11.2 mmol, 1 eq) and (3S)-3-aminobutan-1-ol (1.0 g, 11.2 mmol, 1 eq) in Tol. (20 mL) was added TEA (385.9 mg, 3.8

mmol, 530.9 uL, 0.3 eq). The mixture was stirred at 110°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give (S)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione.

[00586] Step 2: (S)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione

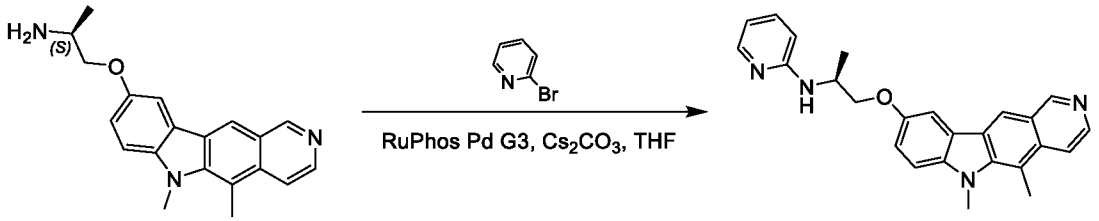
[00587] A mixture of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 eq), (S)-2-(4-hydroxybutan-2-yl)isoindoline-1,3-dione (100.3 mg, 457.4 umol, 1.2 eq), 2-(tributyl-λ5-phosphanylidene) acetonitrile (184.0 mg, 762.4 umol, 2 eq) in Tol. (5 mL) was stirred at 100°C for 12 hr under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (DCM: MeOH = 10/1) to give (S)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione.

[00588] Step 3: (S)-4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine

[00589] To a solution of (S)-2-(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-yl)isoindoline-1,3-dione (120 mg, 258.8 umol, 1 eq) in EtOH (5 mL) was added $N_2H_4.H_2O$ (264.4 mg, 5.1 mmol, 256.7 uL, 98% purity, 20 eq). The mixture was stirred at 80°C for 12 hr. The reaction mixture was filtered to give filtrate. The filtrate was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 7%-37%,9min) to give (S)-4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)butan-2-amine.

[00590] MS (ESI): *m/z* = 334.1 $[M+H]^+$

[00591] **(S)-N-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)pyridin-2-amine (Compound 269)**

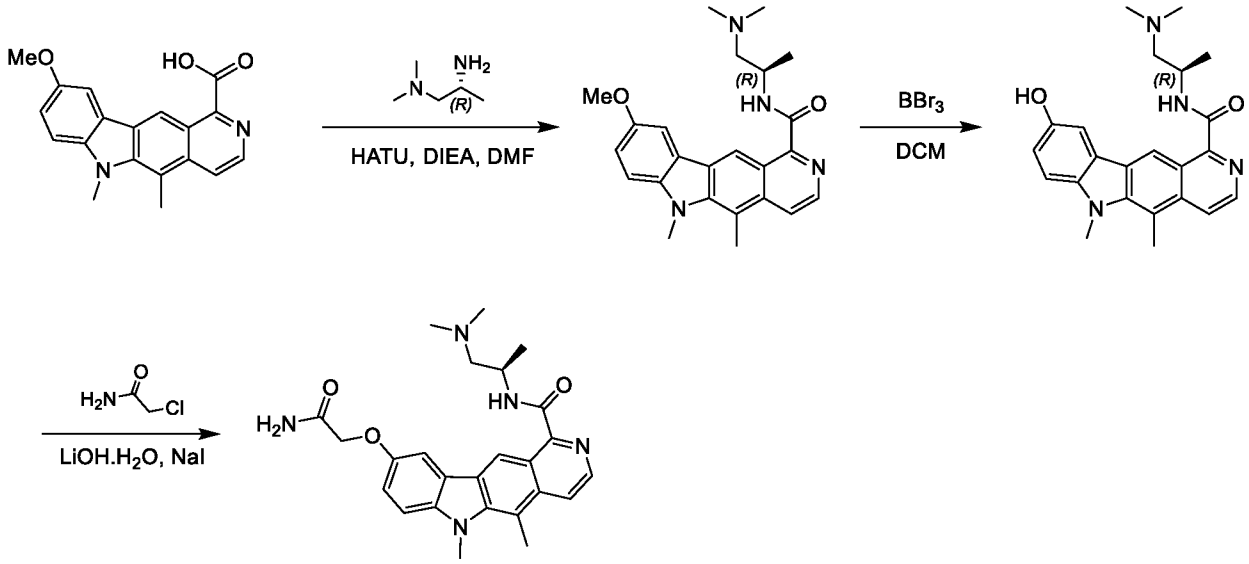


[00592] To a solution of (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxypropan-2-amine (50 mg, 115.3 umol, 1 eq, TFA) in MeOH (5 mL) was added basic resin to adjusted pH = 8. Then the mixture was filtered and concentrated under reduced pressure to give a residue. The residue was dissolve with THF (2 mL) and added 2-bromopyridine (36.4 mg,

230.7 umol, 21.9 uL, 2 eq), Cs_2CO_3 (112.7 mg, 346.0 umol, 3 eq) and RuPhos Pd G3 (9.6 mg, 11.5 umol, 0.1 eq). The mixture was stirred at 100°C for 12 hr under N_2. The mixture was concentrated, and the residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,9min) to afford (S)-N-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)pyridin-2-amine.

[00593] MS (ESI): *m/z* = 397.1 $[M+H]^+$

[00594] **9-(2-amino-2-oxo-ethoxy)-N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (Compound 270)**



[00595] Step 1: N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide

[00596] To a solution of 9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxylic acid (350 mg, 1.0 mmol, 1 *eq*) in DMF (5 mL) was added (2R)-N1,N1-dimethylpropane-1,2-diamine (573.9 mg, 3.2 mmol, 3 *eq*, 2HCl), DIEA (706.0 mg, 5.4 mmol, 951.5 uL, 5 *eq*). Then HATU (830.8 mg, 2.1 mmol, 2 *eq*) was added to the mixture at 0°C. The mixture was warmed to 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition) to give N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

[00597] Step 2: (R)-N-(1-(dimethylamino)propan-2-yl)-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00598] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-methoxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (100 mg, 247.2 umol, 1 *eq*) in DCM (3 mL)

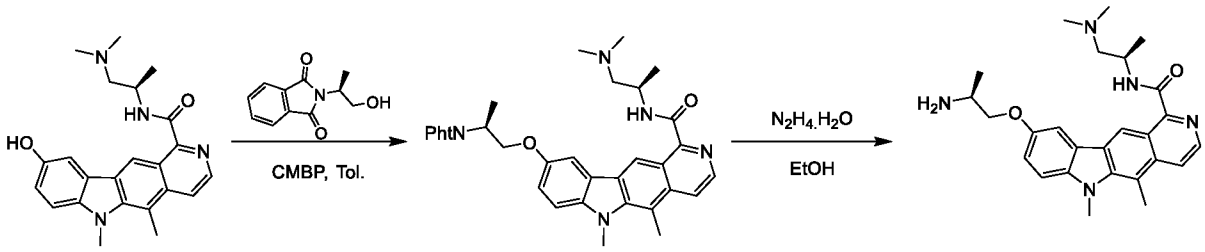
was added BBr_3 (309.6 mg, 1.2 mmol, 119.1 uL, 5 *eq*) at 0°C. The mixture was stirred at 45°C for 1 hr. The reaction mixture was added to $NH_3.H_2O$ (5mL, purity 25%) at 0°C. The water phase was separated, extracted with CH_2Cl_2 (5 mL × 3). The combined organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-hydroxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

[00599] Step 3: (R)-9-(2-amino-2-oxoethoxy)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00600] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-hydroxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (50 mg, 128.0 umol, 1 *eq*) in DMF (2 mL) was added 2-chloroacetamide (10.7 mg, 115.2 umol, 0.9 *eq*), $LiOH.H_2O$ (16.1 mg, 384.1 umol, 3 *eq*) and NaI (19.1 mg, 128.0 umol, 1 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,10min) to give 9-(2-amino-2-oxo-ethoxy)-N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

[00601] MS (ESI): *m/z* = 448.2 $[M+H]^+$

[00602] **9-[(2S)-2-aminopropoxy]-N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (Compound 271)**



[00603] Step 1: N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-[(2S)-2-(1,3-dioxoisoindolin-2-yl)propoxy]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide

[00604] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-hydroxy-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (50 mg, 128.0 umol, 1 *eq*) in Tol. (3 mL) was added 2-[(1S)-2-hydroxy-1-methyl-ethyl]isoindoline-1,3-dione (31.5 mg, 153.6 umol, 1.2 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (61.8 mg, 256.1 umol, 2 *eq*) under N_2. The mixture was stirred at 100°C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2,

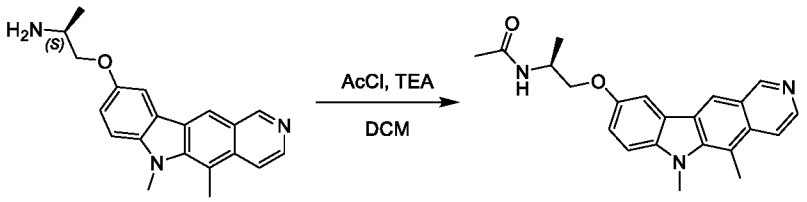
DCM: MeOH = 10:1) to give N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-[(2S)-2-(1,3-dioxoisoindolin-2-yl)propoxy]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

[00605] Step 2: 9-((S)-2-aminopropoxy)-N-((R)-1-(dimethylamino)propan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00606] To a solution of N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-9-[(2S)-2-(1,3-dioxoisoindolin-2-yl)propoxy]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide (20 mg, 34.6 umol, 1 *eq*) in EtOH (2 mL) was added $N_2H_4.H_2O$ (8.8 mg, 173.1 umol, 8.5 uL, 98% purity, 5 *eq*). The mixture was stirred at 70°C for 12 hr. The reaction mixture was concentrated under reduced pressure. The residue was diluted with NH_4Cl 5 mL and extracted with EtOAc (5 mL × 3). The combined organic layers were washed with brine (5 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-35%,10min) to give 9-[(2S)-2-aminopropoxy]-N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxamide.

[00607] MS (ESI): *m/z* = 448.2 $[M+H]^+$

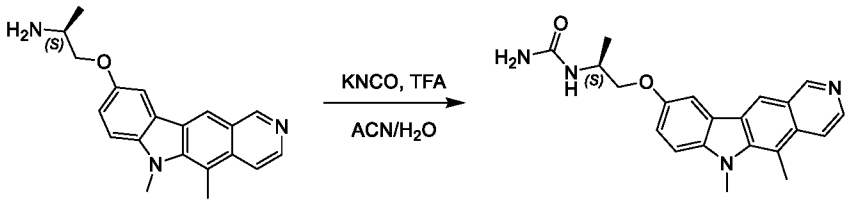
[00608] **(S)-N-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)acetamide (Compound 272)**



[00609] To a solution of (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxypropan-2-amine (50 mg, 115.3 umol, 1 eq, TFA) in DCM (3 mL) was added TEA (35.0 mg, 346.0 umol, 48.1 uL, 3 eq) and acetyl chloride (10.8 mg, 138.4 umol, 9.8 uL, 1.2 eq) at 0°C. The mixture was stirred at 25°C for 1 hr. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 13%-43%,9min) to afford (S)-N-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)acetamide.

[00610] MS (ESI): *m/z* = 362.2 $[M+H]^+$

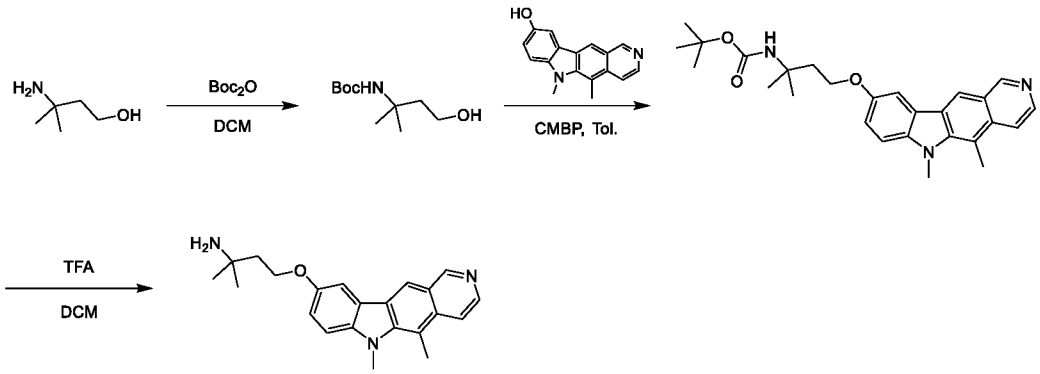
[00611] **(S)-1-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)urea (Compound 273)**



[00612] To a solution of (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxypropan-2-amine (50 mg, 115.3 umol, 1 eq, TFA) in ACN (1 mL) / H_2O (1 mL) was added KNCO (29.4 mg, 346.0 umol, 3 eq) and TFA (13.1 mg, 115.3 umol, 8.5 uL, 1 eq). The mixture was stirred at 40°C for 12 hr. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-35%,8min) to afford (S)-1-(1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)propan-2-yl)urea.

[00613] MS (ESI): *m/z* = 363.1 $[M+H]^+$

[00614] **4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-2-methylbutan-2-amine (Compound 274)**



[00615] Step 1: tert-butyl (4-hydroxy-2-methylbutan-2-yl)carbamate

[00616] tert-Butoxycarbonyl tert-butyl carbonate (1.3 g, 5.8 mmol, 1.3 mL, 1.2 *eq*) and 3-amino-3-methyl-butan-1-ol (0.5 g, 4.8 mmol, 1 *eq*) in DCM (15 mL) was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduce pressure to give tert-butyl (4-hydroxy-2-methylbutan-2-yl)carbamate

[00617] Step 2: tert-butyl(4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-2-methylbutan-2-yl)-carbamate

[00618] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (50 mg, 190.6 umol, 1 *eq*) in toluene (2 mL) was added tert-butyl (4-hydroxy-2-methylbutan-2-yl)carbamate (46.5 mg, 228.7 umol, 1.2 *eq*), and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (92.0 mg, 381.2 umol, 2 *eq*). The reaction mixture was stirred at 100°C for 2 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was

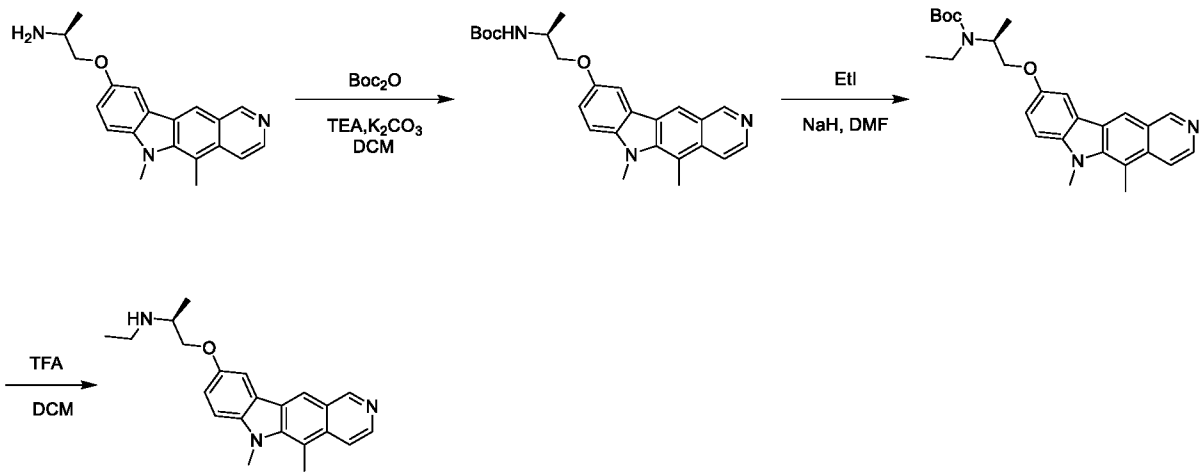
diluted with DCM (2 mL). The residue was purified by prep-TLC (SiO_2, DCM: Methanol = 10:1) to give tert-butyl (4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-2-methylbutan-2-yl)carbamate.

[00619] Step 3: 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-2-methylbutan-2-amine

[00620] To a solution of tert-butyl N-[3-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1,1-dimethyl-propyl]carbamate (82 mg, 183.2 umol, 1 *eq*) in DCM (2 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL, 73.7 *eq*). The reaction mixture was stirred at 25°C for 3 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with methanol (2 mL). The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 5%-25%,8min) to give 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-2-methylbutan-2-amine.

[00621] MS (ESI): *m/z* =348.1 $[M+H]^+$

[00622] **(2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-ethyl-propan-2-amine (Compound 275)**



[00623] Step 1: tert-butylN-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate

[00624] To a solution of (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxypropan-2-amine (200 mg, 626.1 umol, 1 *eq*) in DCM (10 mL) was added TEA (190.0 mg, 1.8 mmol, 261.4 uL, 3 *eq*) and Boc_2O (273.3 mg , 1.2 mmol , 287.7 uL , 2 *eq*). The mixture was stirred at 25°C for 12 hr. The mixture was concentrated to get crude residue and diluted with MeOH 10 mL. Then K_2CO_3 (259.6 mg, 1.8 mmol , 3 *eq*) was added. Then the mixture was stirred at 50°C for 12 hr. The mixture was concentrated to get crude residue and then diluted with H_2O 10 mL and extracted with EtOAc (20 mL × 3). The combined organic layers

were washed with brine (10 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~10% Dichloromethane : Methanol gradient @ 60 mL/min) to afford tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate.

[00625] Step 2: tert-butylN-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-ethyl-carbamate

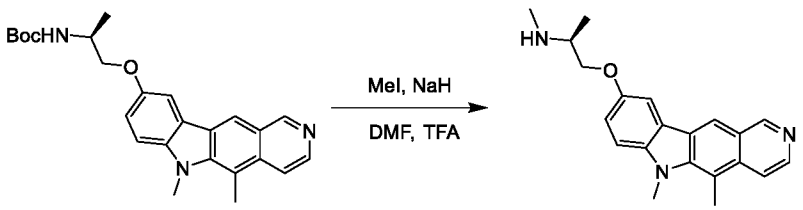
[00626] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate (30 mg, 71.51 umol, 1 *eq*) in DMF (2 mL) was added NaH (8.5 mg , 214.5 umol , 60% purity, 3 *eq*). The mixture was stirred at 0°C for 10 min. Then iodoethane (11.1 mg, 71.5 umol, 5.7 uL, 1 *eq*) was added to the mixture and stirred at 25°C for 1 hr. The mixture was quenched with TFA (0.2 mL) and concentrated to afford tert-butyl-N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl) oxy-1-methyl-ethyl]-N-ethyl-carbamate.

[00627] Step 3: (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-ethyl-propan-2-amine

[00628] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-ethyl-carbamate (30 mg, 67.03 umol, 1 *eq*) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25°C for 1 hr. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 8%-38%,9min) to afford (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-ethyl-propan-2-amine.

[00629] MS (ESI): m/z = 348.1 $[M+H]^+$

[00630] **(S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylpropan-2-amine (Compound 276)**

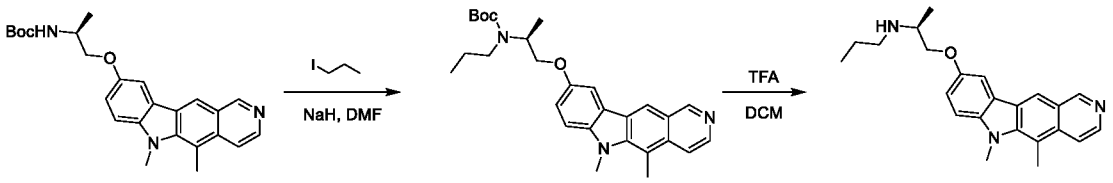


[00631] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate (50 mg, 119.1 umol, 1 eq) in DMF (2 mL) was added NaH (14.3 mg, 357.5 umol, 60% purity, 3 eq). The mixture was stirred at 0°C for 30 min, and then MeI (16.9 mg, 119.1 umol, 7.4 uL, 1 eq) was added. The mixture was stirred at 25°C for 12 hr. The mixture was quenched with TFA (1.0 mL) and concentrated to get crude

residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 1%-25%,8min) to afford (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylpropan-2-amine.

[00632] MS (ESI): *m/z* =334.1 $[M+H]^+$

[00633] **(2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-propyl-propan-2-amine (Compound 277)**



[00634] Step 1: tert-butylN-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-propyl-carbamate

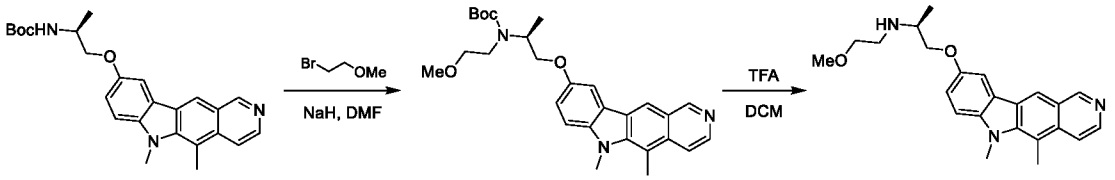
[00635] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate (50 mg, 119.1 umol, 1 eq) in DMF (2 mL) was added NaH (14.3 mg, 357.5 umol , 60% purity, 3 eq). The mixture was stirred at 0°C for 10 min. Then 1-iodopropane (20.2 mg, 119.1 umol, 11.6 ul, 1 eq) was added to the mixture and stirred at 25°C for 1 hr. The reaction mixture was poured into NH_4Cl (10 mL) and extracted with EtOAc (20 mL ×3). The combined organic layers were washed with brine (20 mL ×3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give tert-butylN-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1- methyl-ethyl]-N-propyl-carbamate.

[00636] Step 2: (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-propyl-propan-2-amine

[00637] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-propyl-carbamate (60 mg, 129.98 umol, 1 *eq*) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (**TFA condition,** column: Phenomenex Luna C18 150*30mm*5um; mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,9min) to give (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N-propyl-propan-2-amine.

[00638] MS (ESI): *m/z* = 362.2 $[M+H]^+$

[00639] **(2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N- (2-methoxyethyl)propan-2-amine (Compound 278)**



[00640] Step 1: tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-(2-methoxyethyl)carbamate

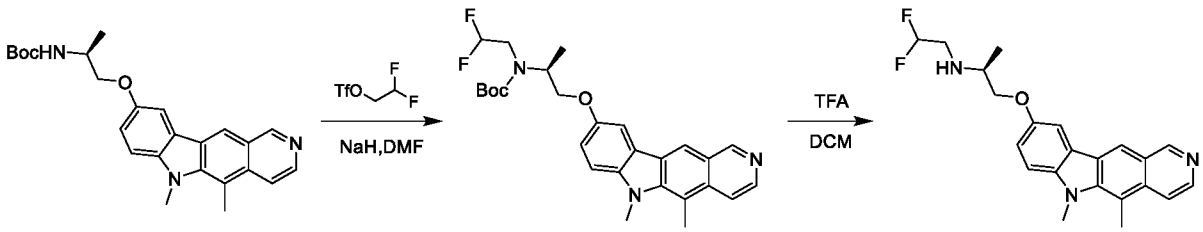
[00641] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate (30 mg, 71.5 umol , 1 *eq*) in DMF (1 mL) was added NaH (8.5 mg , 214.5 umol , 60% purity, 3 *eq*). The mixture was stirred at 0°C for 10 min. Then 1-bromo-2-methoxy-ethane (10.9 mg, 78.6 umol, 7.3 ul , 1.1 *eq*) was added to the mixture and stirred at 25°C for 1 hr. The mixture was quenched with TFA (0.2 mL) and concentrated to afford tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-(2-methoxyethyl)carbamate.

[00642] Step 2: (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-(2-methoxyethyl)propan-2-amine

[00643] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]-N-(2-methoxyethyl)carbamate (30 mg, 62.8 umol, 1 *eq*) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25°C for 1 hr. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 8%-38%,9min) to afford (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-N- (2-methoxyethyl)propan-2-amine.

[00644] MS (ESI): m/z = 378.1 $[M+H]^+$

[00645] **(2S)-N-(2,2-difluoroethyl)-1-(5,6- dimethylpyrido[4,3-b]carbazol-9-yl)oxy-propan-2-amine (Compound 279)**



[00646] Step 1: tert-butylN-(2,2-difluoroethyl)-N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate

[00647] To a solution of tert-butyl N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy- 1-methyl-ethyl]carbamate (50 mg , 119.1 umol, 1 *eq*) in DMF (2 mL) was added NaH

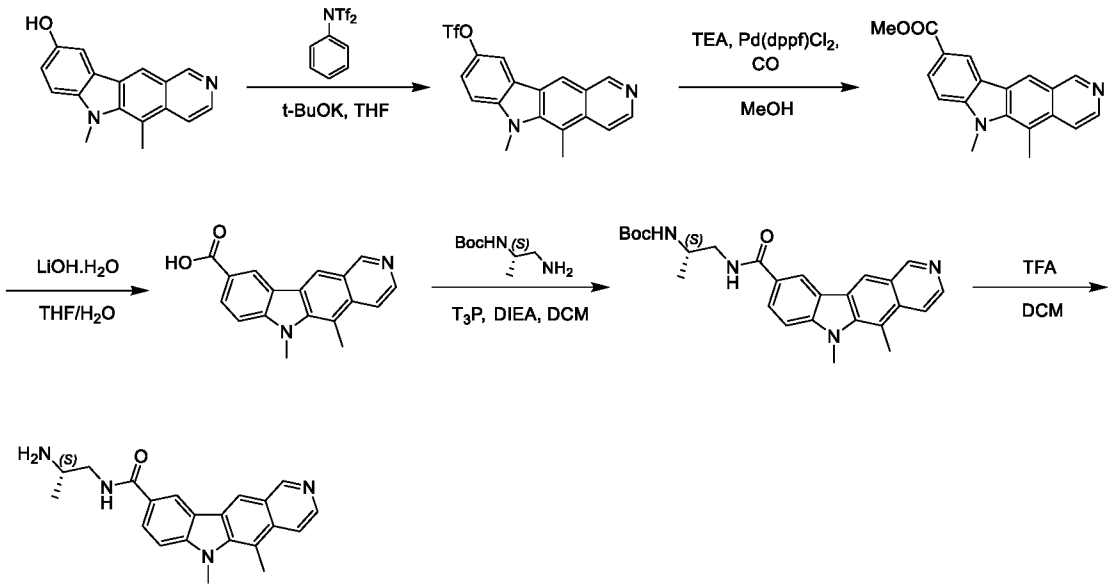
(14.3 mg , 357.5 umol , 60% purity, 3 *eq*). The mixture was stirred at 0°C for 10 min. Then 2,2-difluoroethyl trifluoromethanesulfonate (25.5 mg, 119.1 umol , 5.7 uL, 1 *eq*) was added to the mixture and stirred at 25°C for 1 hr. The mixture was poured into NH_4Cl (5 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with brine (5 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2 , DCM: MeOH = 10:1) to give tert-butyl N-(2,2-difluoroethyl)-N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy -1-methyl-ethyl]carbamate.

[00648] Step 2: (2S)-N-(2,2-difluoroethyl)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-propan-2-amine

[00649] To a solution of tert-butyl N-(2,2-difluoroethyl)-N-[(1S)-2-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxy-1-methyl-ethyl]carbamate (20 mg, 41.3 umol, 1 *eq*) in DCM (2 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL, 326.5 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated to dryness. The residue was purified by prep-HPLC to give (2S)-N-(2,2-difluoroethyl)-1-(5,6- dimethylpyrido[4,3-b]carbazol-9-yl)oxy-propan-2-amine.

[00650] MS (ESI): *m/z* = 384.2$[M+H]^+$

[00651] **(S)-N-(2-aminopropyl)-5,6- dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 280)**



[00652] Step 1: 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate

[00653] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (500 mg, 1.9 mmol, 1 *eq*) in THF (20 mL) was added t-BuOK (1 M, 3.8 mL, 2 *eq*) at 0°C. The mixture was stirred at 0°C for 10 min. 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl) methanesulfonamide

(817.1 mg, 2.3 mmol, 1.2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl trifluoromethanesulfonate.

[00654] Step 2: methyl 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylate

[00655] To a solution of (5,6-dimethylpyrido[4,3-b]carbazol-9-yl) trifluoromethanesulfonate (570 mg, 1.5 mmol, 1 *eq*) in MeOH (15 mL) was added TEA (438.8 mg, 4.3 mmol, 603.5 uL, 3 *eq*) and $Pd(dppf)Cl_2$ (105.8 mg, 144.5 umol, 0.1 *eq*). The mixture was stirred at 75°C for 4 hr under CO (50 psi). The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H_2O 30 mL and extracted with DCM (30 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 10 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ethergradient @ 80 mL/min) to give methyl 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylate.

[00656] Step 3: 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylic acid

[00657] To a solution of methyl 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylate (200 mg, 657.2 umol, 1 *eq*) in THF (1.5 mL) / H_2O (0.5 mL) was added $LiOH.H_2O$ (110.3 mg, 2.63 mmol, 4 *eq*). The reaction mixture was stirred at 60°C for 12 hr. The pH was adjusted to 5 by addition HCl (1 M), then filtered and concentrated under reduced pressure to give 5,6-dimethylpyrido [4,3-b]carbazole-9-carboxylic acid.

[00658] Step 4: (S)-tert-butyl(1-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propan-2-yl)carbamate

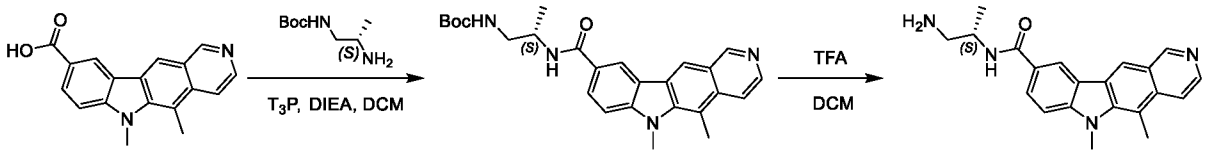
[00659] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (44 mg, 151.6 umol, 1 *eq*) in DCM (2 mL) was added tert-butyl N-[(1S)-2-amino-1-methyl-ethyl] carbamate (52.8 mg, 303.1 umol, 2 *eq*), T_3P (192.9 mg, 303.1 umol, 180.3 uL, 50% purity, 2 *eq*) and DIEA (39.2 mg, 303.1 umol, 52.8 uL, 2 *eq*) at 0°C under N_2. The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give (S)-tert-butyl(1-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propan-2-yl)carbamate.

[00660] Step 5: (S)-N-(2-aminopropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide

[00661] To a solution of tert-butyl N-[(1S)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl) amino]-1-methyl-ethyl]carbamate (40 mg, 89.6 umol, 1 *eq*) in DCM (2 mL) was added TFA (10.2 mg, 89.6 umol, 6.6 uL, 1 *eq*). The reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with methanol (2 mL). The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150×30 mm×5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 1%-28%,9min) to give (S)-N-(2-aminopropyl)-5,6- dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00662] MS (ESI): *m/z* =347.1 $[M+H]^+$

[00663] **(S)-N-(1-aminopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 281)**



[00664] Step 1: (S)-tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propyl)carbamate

[00665] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylic acid (40 mg, 137.7 umol, 1 *eq*) in DCM (2 mL) was added tert-butyl N-[(2S)-2-aminopropyl]carbamate (48.0 mg, 275.5 umol, 2 *eq*), T_3P (175.3 mg, 275.5 umol, 163.8 uL, 50% purity, 2 *eq*) and DIEA (35.6 mg, 275.5 umol, 48.0 uL, 2 *eq*) at 0°C under N_2. The reaction mixture was stirred at 25°C for 1 hr. T_3P (87.6 mg, 137.7 umol, 81.9 uL, 50% purity, 1 *eq*) and DIEA (17.8 mg, 137.7 umol, 24.0 uL, 1 *eq*) was added to the solution and the reaction was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10: 1) to give (S)-tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propyl)carbamate.

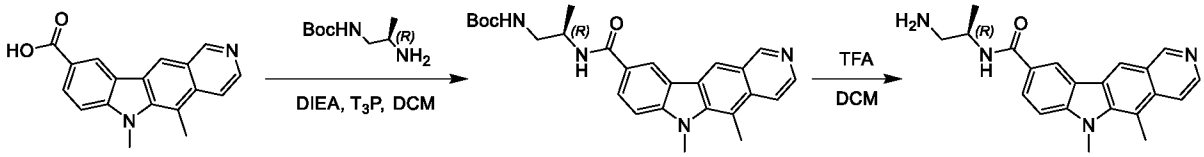
[00666] Step 2: (S)-N-(1-aminopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide

[00667] To a solution of (S)-tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propyl)carbamate (55 mg, 123.1 umol, 1 *eq*) in DCM (2 mL) was added TFA (1 mL). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove **solvent**. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-28%,9min). The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-

35%,8min) to give (S)-N-(1-aminopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00668] MS (ESI): *m/z* = 347.1 $[M+H]^+$

[00669] **N-[(1R)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b] carbazole-9-carboxamide (Compound 282)**



[00670] Step 1: tert-butyl N-[(2R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]propyl]carbamate

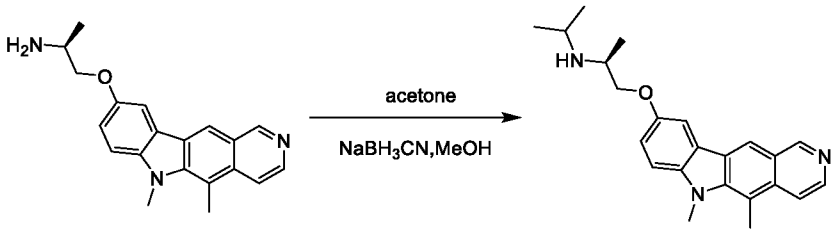
[00671] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg, 103.3 umol, 1 eq) and tert-butyl N-[(2R)-2-aminopropyl]carbamate (45.0 mg, 258.3 umol, 2.5 eq) in DCM (3 mL) was added T_3P (131.5 mg, 206.6 umol, 122.9 uL, 50% purity, 2 eq) cooled to 0°C. Then DIEA (40.0 mg, 310.0 umol, 54.0 uL, 3 eq) was added. The mixture was stirred at 25°C for 12 hr under N_2. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-TLC (SiO_2, Dichloromethane : Methanol=10/1) to give tert-butyl N-[(2R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]propyl]carbamate.

[00672] Step 2: N-[(1R)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

[00673] To a solution of tert-butyl N-[(2R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl) amino]propyl]carbamate (40 mg, 89.5 umol, 1 eq) in DCM (2 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL, 150.7 eq). The mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 80*40mm*3 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-25%,7min) to give N-[(1R)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b] carbazole-9-carboxamide.

[00674] MS (ESI): *m/z* = 347.1 $[M+H]^+$

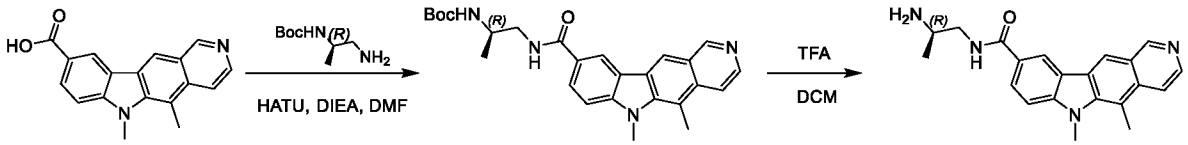
[00675] **(S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-isopropylpropan-2-amine (Compound 283)**



[00676] To a solution of (2S)-1-(5,6-dimethylpyrido[4,3-b]carbazol-9-yl)oxypropan-2-amine (40 mg, 112.4 umol, 1 eq, HCl) in MeOH (1 mL) was added TEA adjusted pH to 8 and then acetone (9.7 mg, 168.6 umol, 12.4 uL, 1.5 eq) was added. AcOH was added to the above mixture was adjusted pH to 5 and then $NaBH_3CN$ (28.2 mg, 449.6 umol, 4 eq) was added. The mixture was stirred at 30°C for 12 hr. The reaction was filtered and the filtrated was concentrated to give a residue. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-25%,8min) to afford (S)-1-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-isopropylpropan-2-amine.

[00677] MS (ESI): *m/z* =362.2 $[M+H]^+$

[00678] **(R)-N-(2-aminopropyl)-5,6- dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 284)**



[00679] Step 1: (R)-tert-butyl-(1-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamido)propan-2-yl)carbamate

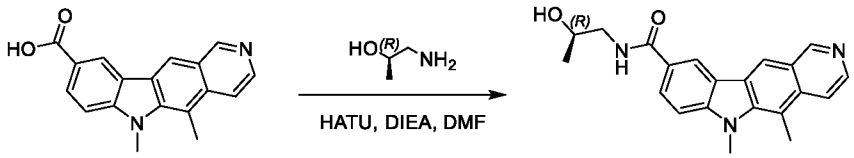
[00680] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg, 103.3 umol, 1 *eq*) in DMF (2 mL) was added DIEA (40.1 mg, 310.0 umol, 54.0 uL, 3 *eq*) and HATU (58.9 mg, 155.0 umol, 1.5 *eq*). The reaction mixture was stirred at 25°C for 30 min. tert-Butyl N-[(1R)-2-amino-1-methyl-ethyl]carbamate (36.0 mg, 206.7 umol, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 3 hr. The reaction mixture was concentrated under reduced pressure to remove DMF. The residue was diluted with H_2O (15 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layers were washed with brine (15 mL × 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give (R)-tert-butyl-(1-(5,6-dimethyl-6H- pyrido[4,3-b]carbazole-9-carboxamido)propa-n-2-yl)carbamate.

[00681] Step 2: (R)-N-(2-aminopropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide

[00682] To solution of tert-butyl N-[(1R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl) amino]-1-methyl-ethyl]carbamate (40 mg, 89.58 umol, 1 *eq*) in DCM (2 mL) was added TFA (102.1 mg, 895.8 umol, 66.3 uL, 10 *eq*). The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30 mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-30%,9 min) to give (R)-N-(2-aminopropyl)-5,6- dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00683] MS (ESI): *m/z* =347.1 $[M+H]^+$

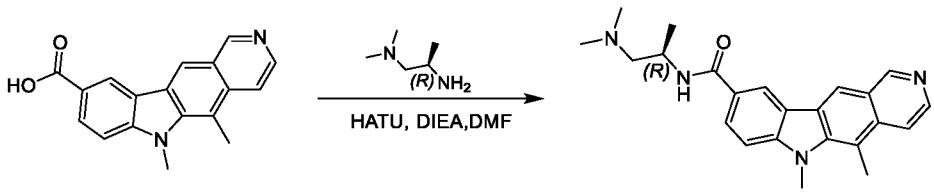
[00684] **(R)-N-(2-hydroxypropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 285)**



[00685] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 eq) in DMF (2 mL) was added (2R)-1-aminopropan-2-ol (25.8 mg, 344.4 umol, 27.1 uL, 2 eq), DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 eq) and HATU (98.2 mg, 258.3 umol, 1.5 eq) at 0°C under N_2. The reaction mixture was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition;column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-35%,9min) to give (R)-N-(2-hydroxypropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00686] MS (ESI): *m/z* =348.1 $[M+H]^+$

[00687] **N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (Compound 286)**

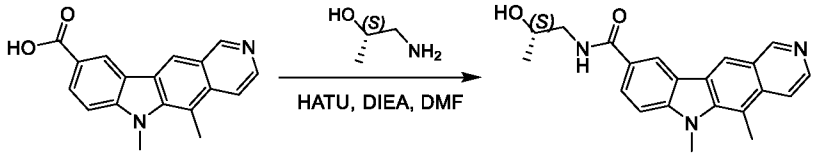


[00688] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg, 103.3 umol, 1 *eq*) in DMF (3 mL) was added DIEA (33.3 mg, 258.3 umol, 45.0 uL, 2.5 *eq*) and HATU (39.2 mg, 103.3 umol, 1 *eq*) and stirred at 25°C for 30 min. The mixture was

added (2R)-N1,N1-dimethylpropane-1,2-diamine (21.7 mg, 124.0 umol, 1.2 *eq*, 2HCl) and stirred at 25°C for 2 hr. The reaction mixture was filtered. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,9min) to give N-[(1R)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

[00689] MS (ESI): *m/z* = 375.1 $[M+H]^+$

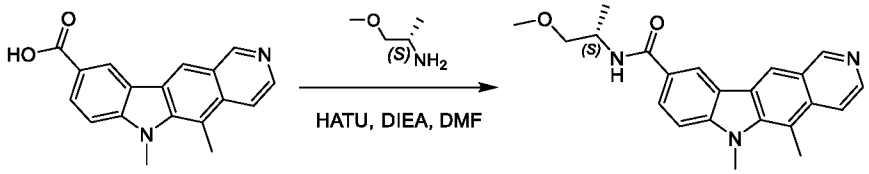
[00690] **N-[(2S)-2-hydroxypropyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (Compound 287)**



[00691] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg, 103.3 umol, 1 *eq*) in DMF (3 mL) was added DIEA (33.3 mg, 258.3 umol, 45.0 uL, 2.5 *eq*) and HATU (39.2 mg, 103.3 umol, 1 *eq*) and stirred at 25°C for 30 min. (2S)-1-aminopropan-2-ol (9.3 mg, 124.0 umol, 9.7 uL, 1.2 *eq*) was added to the above mixture and the mixture was stirred at 25°C for 12 hr. The reaction mixture was filtered. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,9min) to give N-[(2S)-2-hydroxypropyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

[00692] MS (ESI): *m/z* = 348.0 $[M+H]^+$

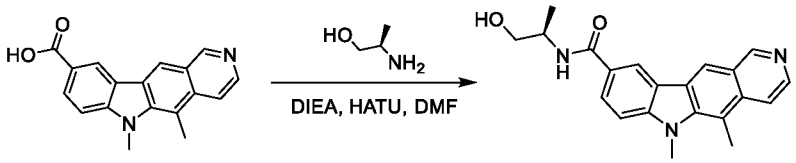
[00693] **(S)-N-(1-methoxypropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 288)**



[00694] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*) and HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred for 30 min. (2S)-1-methoxypropan-2-amine (30.7 mg, 344.4 umol, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-37%,8min) to give (S)-N-(1-methoxypropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00695] MS (ESI): *m/z* = 362.2 $[M+H]^+$

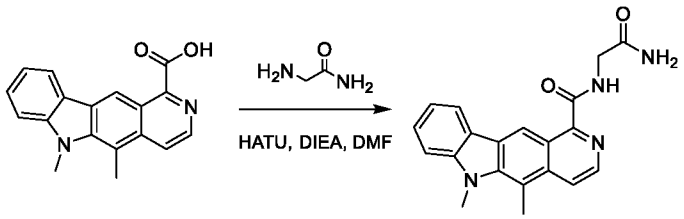
[00696] **(R)-N-(1-hydroxypropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 289)**



[00697] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg, 103.3 umol, 1 *eq*) in DMF (2 mL) was added DIEA (40.0 mg, 310.0 umol, 54.0 uL, 3 *eq*), HATU (58.9 mg, 155.0 umol, 1.5 *eq*) and stirred for 30 min. (2R)-2-aminopropan-1-ol (15.5 mg, 206.6 umol, 16.1 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-30%,8min) to give (R)-N-(1-hydroxypropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00698] MS (ESI): *m/z* = 348.2 $[M+H]^+$

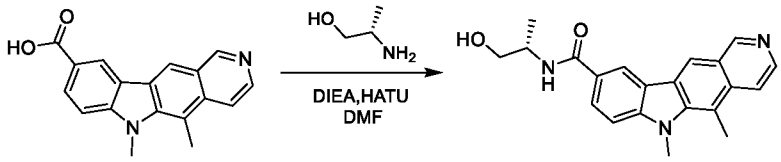
[00699] **N-(2-amino-2-oxoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 290)**



[00700] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*), HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred for 30 min. 2-aminoacetamide (38.0 mg, 344.4 umol, 2 *eq*, HCl) was added to the solution and stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-45%,10min) to give N-(2-amino-2-oxoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00701] MS (ESI): *m/z* = 347.1 $[M+H]^+$

[00702] **N-[(1S)-2-hydroxy-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (Compound 291)**



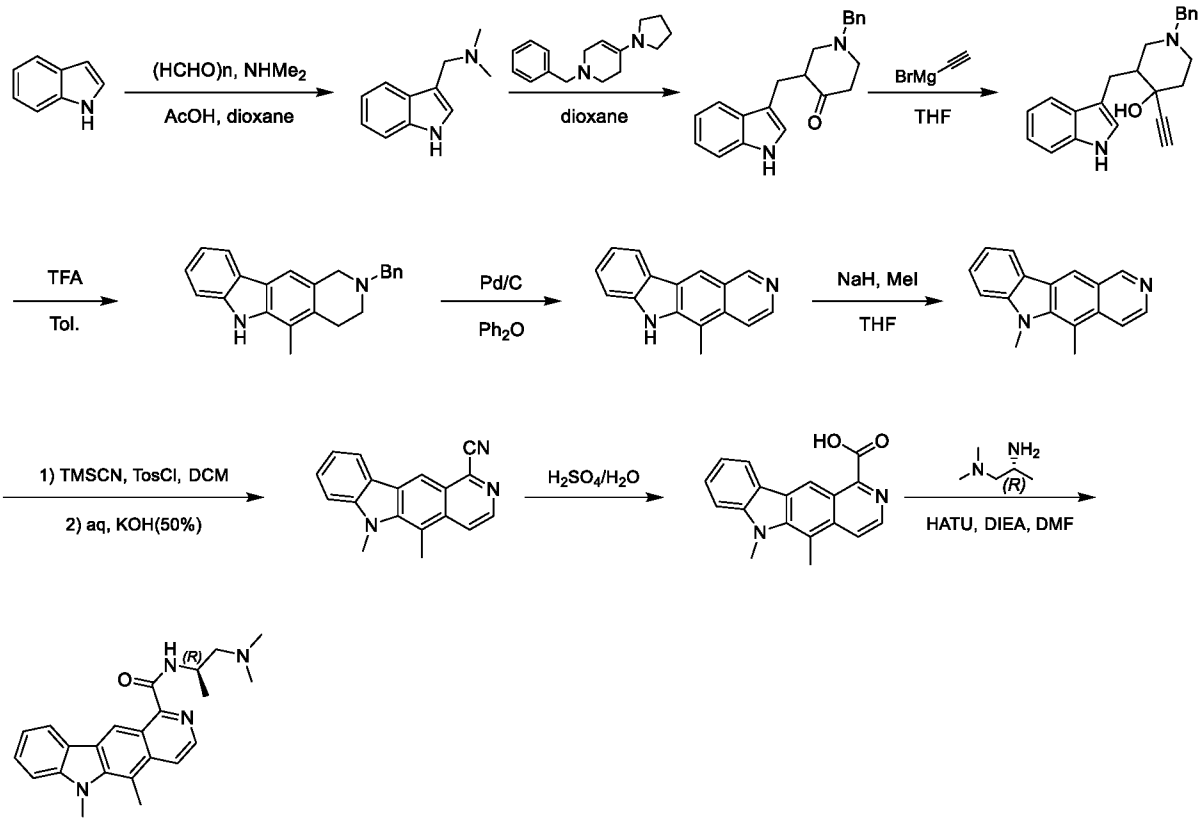
[00703] N-[(1S)-2-hydroxy-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

[00704] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (30 mg , 103.3 umol , 1 *eq*) in DMF (2 mL) was added DIEA (40.0 mg , 310.0 umol , 54.0 uL, 3 *eq*) and HATU (58.9 mg, 155.0 umol , 1.5 *eq*) and stirred for 30 min. (2S)-2-aminopropan-1-ol (9.3 mg, 124.0 umol, 9.6 ul , 1.2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 6 hr. The reaction mixture was concentrated to dryness. The crude product was purified by reversed-phase HPLC(0.1% $NH_3.H_2O$ condition column: Phenomenex Gemini-NX C18 75*30mm*3um ; mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 25%-55%,8min) to give N-[(1S)-2-hydroxy-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (12.3 mg, 35.0umol, 33.9% yield, 99.29% purity) as a yellow solid.

[00705] ^{1}HNMR (400MHz, METHANOL-d_4) δ 9.32 (s, 1H), 8.81 (d, *J* = 1.6 Hz, 1H), 8.75 (s, 1H), 8.39 (br d, *J* = 6.4 Hz, 1H), 8.18 - 8.07 (m, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 4.34 - 4.27 (m, 1H), 4.24 (s, 3H), 3.70 (dq, *J* = 5.8, 10.8 Hz, 2H), 3.15 (s, 3H), 1.35 (d, *J* = 6.8 Hz, 3H)

[00706] MS (ESI): *m/z* = 348.2 $[M+H]^+$

[00707] **(R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 292)**



[00708] Step 1: 1-(1H-indol-3-yl)-N,N-dimethylmethanamine

[00709] To a solution of indole (25 g, 213.4 mmol, 1 *eq*) in dioxane (283 mL) and H_2O (283 mL) was added dimethylamine hydrochloride (19.1 g, 234.7 mmol, 1.1 *eq*), formaldehyde(19.0 g, 234.7 mmol, 17.4 mL, 37% purity, 1.1 *eq*), TEA (23.7 g, 234.7 mmol, 32.6 mL, 1.1 *eq*) and AcOH (19.2 g, 320.1 mmol, 18.3 mL, 1.5 *eq*). The mixture was stirred at 30°C for 12 hr. The mixture was concentrated to remove the dioxane and poured into NaOH (1000 mL, 2 N) and solid was separated out. The mixture was filtered and wash with H_2O (500 mL) and the cake was collected to give 1-(1H-indol-3-yl)-N,N-dimethyl-methanamine.

[00710] Step 2: 3-((1H-indol-3-yl)methyl)-1-benzylpiperidin-4-one

[00711] To a solution of 1-(1H-indol-3-yl)-N,N-dimethyl-methanamine (15 g, 86.0 mmol, 1 *eq*) in dioxane (400 mL) was added 1-benzyl-4-pyrrolidin-1-yl-3,6-dihydro-2H-pyridine (52.1 g, 215.2 mmol, 2.5 *eq*). The mixture was stirred at 120°C for 12 hr. The mixture was concentrated to get crude residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate / Petroleum ether gradient @ 60 mL/min) to give 3-((1H-indol-3-yl)methyl)-1-benzylpiperidin-4-one.

[00712] Step 3: 3-((1H-indol-3-yl)methyl)-1-benzyl-4-ethynylpiperidin-4-ol

[00713] To a solution of 3-((1H-indol-3-yl)methyl)-1-benzylpiperidin-4-one (19 g, 59.6 mmol, 1 *eq*) in THF (150 mL) was added bromo(ethynyl)magnesium (0.5 M, 477.3 mL, 4 *eq*). The mixture was stirred at 0°C for 1 hr. The reaction mixture was quenched by addition NH_4Cl (500 mL) at 25°C, and extracted with EtOAc (100 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 3-((1H-indol-3-yl)methyl)-1-benzyl-4-ethynylpiperidin-4-ol.

[00714] Step 4: 2-benzyl-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00715] To a solution of 3-((1H-indol-3-yl)methyl)-1-benzyl-4-ethynylpiperidin-4-ol (20.5 g, 59.5 mmol, 1 *eq*) in toluene (440 mL) was added TFA (67.8 g, 595.1 mmol, 44.0 mL, 10 *eq*). The mixture was stirred at 80°C for 12 hr. The mixture was concentrated to get crude residue and diluted with EtOAc 500 mL and adjusted pH = 8 with sat $NaHCO_3$ extracted with EtOAc (500 mL × 3). The combined organic layers were washed with brine (500 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The mixture was diluted with EtOAc 500 mL and filtered and collect the solid to afford 2-benzyl-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

[00716] Step 5: 5-methyl-6H-pyrido[4,3-b]carbazole

[00717] To a solution of Pd/C (2 g, 10% purity) in Ph_2O (50 mL) was added 2-benzyl-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (4 g, 12.2 mmol, 1 *eq*). The mixture was stirred at 220°C for 4 hr. The reaction mixture was filtered and washed with the solvent (DCM:MeOH = 10:1, 200 mL × 3) and the filtrate dried in vacuum to give crude product. The residue was purified by flash silica gel chromatography (ISCO®;20 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM @ 150 mL/min) to give 5-methyl-6H-pyrido[4,3-b]carbazole.

[00718] Step 6: 5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00719] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazole (2 g, 8.6 mmol, 1 *eq*) in THF (30 mL) was added NaH (1.0 g, 25.8 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. MeI (1.2 g, 8.6 mmol, 536.0 uL, 1 *eq*) was added to the mixture. The mixture was stirred at 25°C for 2 hr. The reaction mixture was partitioned between NH_4Cl 50 mL and EtOAc 50 mL. The water phase was separated, extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;4 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH / DCM gradient @100 mL/min) to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazole.

[00720] Step 7: 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00721] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole (600 mg, 2.7 mmol, 1 *eq*) in DCM (40 mL) was added TMSCN (712.1 mg, 7.1 mmol, 897.9 uL, 2.6 *eq*). To this mixture a solution of TosCl (1.0 g, 5.2 mmol, 1.9 *eq*) in DCM (10 mL) was added at 25 °C. Then the mixture was stirred at 30°C for 12 hr. Then, 10 mL KOH (50% W/W) was added and NH_4HSO_4 (15 mg). The mixture was stirred at 25°C for 2 hr. LCMS showed the reaction was completed and desired product. The mixture was extracted with DCM (100 mL × 3). The combined organic layers were washed with brine (100 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

[00722] Step 8: 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

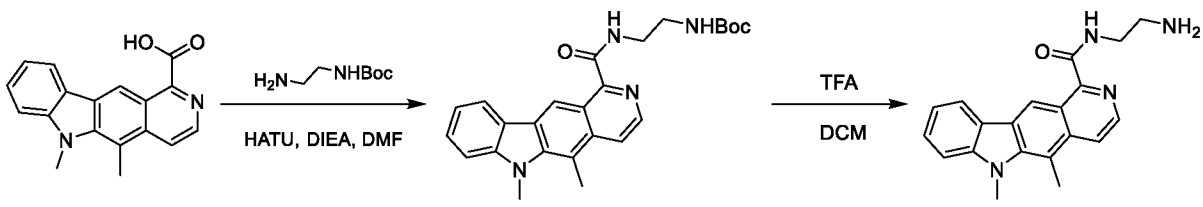
[00723] A mixture of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (100 mg, 368.5 umol, 1 *eq*) in H_2O (2 mL) and H_2SO_4 (1 mL, 98% purity) was stirred at 110°C for 40 hr. The reaction mixture was added to $NaHCO_3$ (100 mL) and concentrated under reduced pressure to give 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

[00724] Step 9: (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00725] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*), HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred for 30 min. (2R)-N1,N1-dimethylpropane-1,2- diamine (60.3 mg, 344.4 umol, 2 *eq*, 2 HCl) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-35%,9min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00726] MS (ESI): *m/z* = 375.2 $[M+H]^+$

[00727] **N-(2-aminoethyl)-5,6-dimethyl-6H- pyrido[4,3-b]carbazole-1-carboxamide (Compound 293)**



[00728] Step 1: tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate

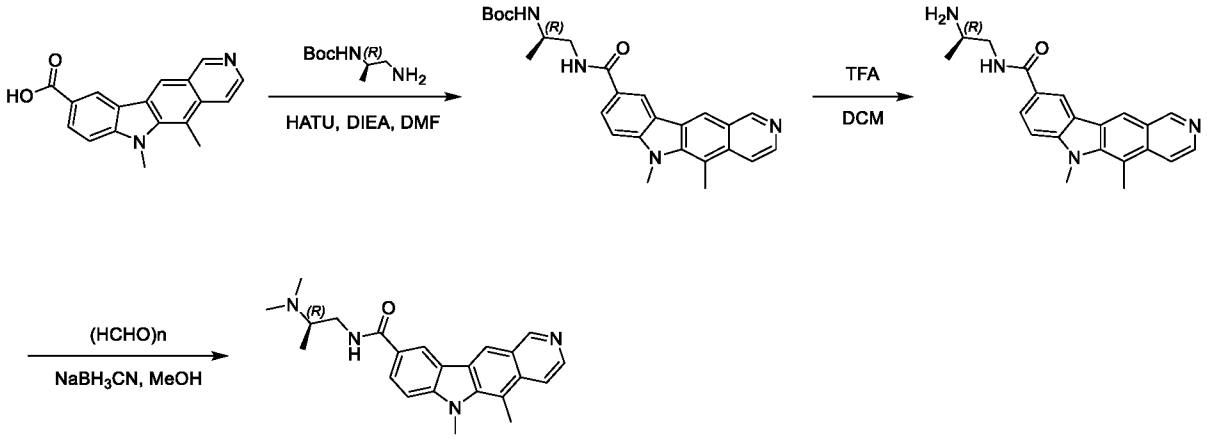
[00729] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-1-carboxylic acid (80 mg, 275.5 umol, 1 *eq*) in DMF (3 mL) was added DIEA (106.8 mg, 826.6 umol, 143.9 uL, 3 *eq*), HATU (157.1 mg, 413.3 umol, 1.5 *eq*) and stirred for 30 min. tert-butyl N-(2-aminoethyl)carbamate (88.3 mg, 551.1 umol, 86.5 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction was added to H_2O (20 mL) and filtered, and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido) ethyl)carbamate.

[00730] Step 2: N-(2-aminoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00731] A mixture of tert-butyl (2-(5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl) carbamate (60 mg, 138.7 umol, 1 *eq*) in TFA (2 mL) and DCM (1 mL) was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,8min) to give N-(2-aminoethyl)-5,6-dimethyl-6H- pyrido[4,3-b]carbazole-1-carboxamide.

[00732] MS (ESI): *m/z* = 333.1 $[M+H]^+$

[00733] **N-[(2R)-2-(dimethylamino)propyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (Compound 294)**



[00734] Step 1: tert-butylN-[(1R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]-1-methyl-ethyl]carbamate

[00735] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (200 mg , 688.9 umol, 1 *eq*) in DMF (4 mL) was added DIEA (89.0 mg, 688.9 umol , 119.9 uL, 1 *eq*) and HATU (261.9 mg, 688.9 umol, 1 *eq*), the mixture was stirred for 30 min. tert-butyl N-

[(1R)-2-amino-1-methyl-ethyl]carbamate (240.0 mg , 1.3 mmol, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 12 hr. The residue was partitioned between H_2O (5mL) and Dichloromethane (5 mL). The mixture was extracted with Dichloromethane (5mL × 3). The separated organic layer was washed with brine (5 mL × 3), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by prep-TLC (SiO_2 , Dichloromethane : Methanol =10/1) to give tert-butyl N-[(1R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]-1-methyl-ethyl]carbamate.

[00736] Step 2: N-[(2R)-2-aminopropyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

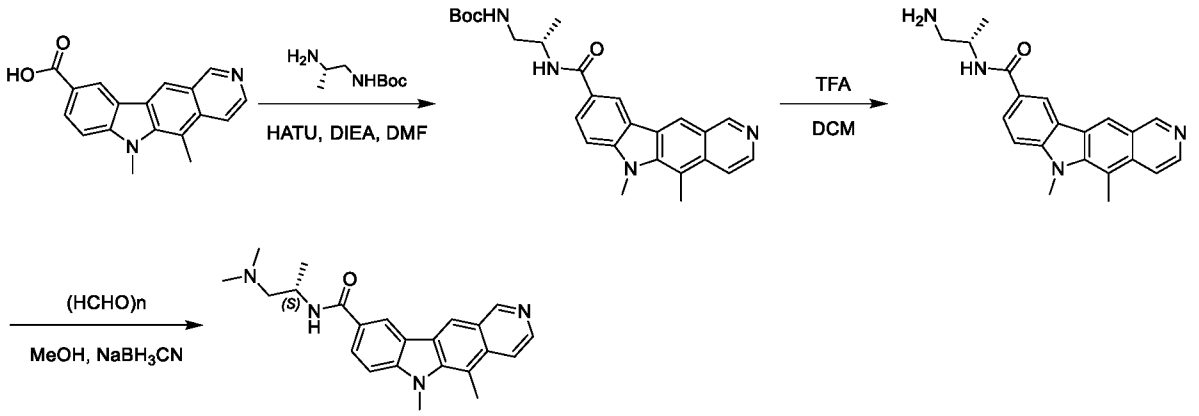
[00737] To a solution of tert-butyl N-[(1R)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]-1-methyl-ethyl]carbamate (70 mg, 156.76 umol, 1 *eq*) in DCM (2 mL) and was added TFA (1.5 g, 13.5 mmol , 1 mL , 86.1 *eq*). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was concentrated to dryness to give N-[(2R)-2-aminopropyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

[00738] Step 3: N-[(2R)-2-(dimethylamino)propyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

[00739] To a solution of N-[(2R)-2-aminopropyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (54 mg, 155.8 umol, 1 *eq*) in MeOH (2 mL) was added TEA to the above mixture was adjusted pH to 8 and was added (HCHO)n (29.9 mg, 311.7 umol , 2 *eq*). AcOH was added to the above mixture was adjusted pH to 5. $NaBH_3CN$ (19.5 mg , 311.7 umol, 2 *eq*) was added to the mixture. The mixture was stirred at 25 °C for 12 hr. The reaction mixture was concentrated to dryness. The crude product was purified by reversed-phase HPLC (TFA condition column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 7%-27%,8min) to give N-[(2R)-2-(dimethylamino)propyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

[00740] MS (ESI): *m/z* = 375.2 $[M+H]^+$

[00741] **N-[(1S)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (Compound 295)**



[00742] Step 1: tert-butyl N-[(2S)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]propyl]carbamate

[00743] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*) and HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and the mixture was stirred at 25°C for 30 min. tert-butyl N-[(2S)-2-aminopropyl]carbamate (60.0 mg, 344.4 umol, 2 *eq*) was added to the mixture and stirred at 25°C for 12 hr. The reaction mixture was partitioned between H_2O 5 mL and CH_2Cl_2 5 mL. The water phase was separated, extracted with CH_2Cl_2 (5 mL × 3). The combined organic phase was washed with brine (10 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, DCM: MeOH = 10:1) to give tert-butyl N-[(2S)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]propyl]carbamate.

[00744] Step 2: N-[(1S)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

[00745] The mixture of tert-butyl N-[(2S)-2-[(5,6-dimethylpyrido[4,3-b]carbazole-9-carbonyl)amino]propyl]carbamate (50 mg, 111.9 umol, 1 *eq*) in DCM (2 mL) and TFA (1 mL) was stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent to give N-[(1S)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

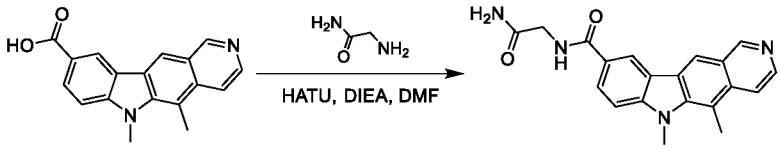
[00746] Step 3: N-[(1S)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide

[00747] To a solution of N-[(1S)-2-amino-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide (50 mg, 144.3 umol, 1 *eq*) in MeOH (3 mL) was added TEA to adjust PH to 8, $(HCHO)_n$ (55.4 mg, 577.3 umol, 4 *eq*), AcOH to adjust PH to 5. The mixture was stirred at 25°C for 30 min. $NaBH_3CN$ (18.1 mg, 288.6 umol, 2 *eq*) was added to the mixture and the mixture stirred at 25°C for 12 hr. The reaction mixture was filtered. The

residue was purified by prep-HPLC (TFA condition;column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-35%,9min). The residue was purified by prep-HPLC (neutral condition;column: Waters Xbridge BEH C18 100*30mm*10um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 15%-45%,8min) to give N-[(1S)-2-(dimethylamino)-1-methyl-ethyl]-5,6-dimethyl-pyrido[4,3-b]carbazole-9-carboxamide.

[00748] MS (ESI): *m/z* = 375.1 $[M+H]^+$

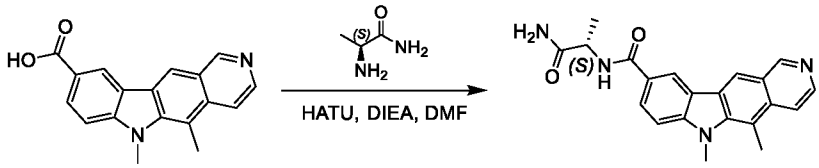
[00749] **N-(2-amino-2-oxoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 296)**



[00750] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (40 mg, 137.8 umol, 1 *eq*) in DMF (2 mL) was added DIEA (53.4 mg, 413.3 umol, 72.0 uL, 3 *eq*) and HATU (78.6 mg, 206.7 umol, 1.5 *eq*). The reaction mixture was sitrred at 25°C for 30 min. 2-aminoacetamide (22.9 mg, 206.7 umol, 1.5 *eq*, HCl) was added to the mixture. The reaction mixture was stirred at 25°C for 3 hr. The residue was filtered, and the filtrate was obtained as brown liquid and purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40 mm*5 um; mobile phase: water (0.1%TFA)-ACN]; B%: 1%-30%,8 min) to give N-(2-amino-2-oxoethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9- carboxamide.

[00751] MS (ESI): *m/z* =347.1 $[M+H]^+$

[00752] **(S)-N-(1-amino-1-oxopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 297)**

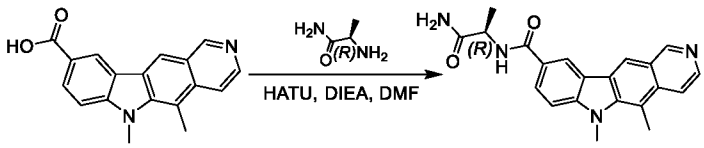


[00753] To a solution of 5, 6-dimethylpyrido[4, 3-b]carbazole-9-carboxylic acid (40 mg, 137.8 umol, 1 *eq*) in DMF (2 mL) added HATU (78.6 mg, 206.7 umol, 1.5 *eq*), DIEA (53.4 mg, 413.3 umol, 72.0 uL, 3 *eq*), (2S)-2-aminopropanamide;hydrochloride (25.7 mg, 206.7 umol, 1.5 *eq*). The reaction mixture was stirred at 25°C for 2 hr. The reaction mixture was filtered. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100×40 mm×5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-30%, 8 min) to

afford (S)-N-(1-amino-1-oxopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00754] MS (ESI): m/z = 361.1[M+H]+

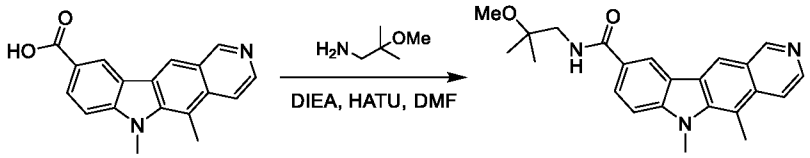
[00755] **(R)-N-(1-amino-1-oxopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 298)**



[00756] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.8 mg, 516.7 umol, 90.0 uL, 3 *eq*) and HATU (98.2 mg, 258.3 umol, 1.5 *eq*). The reaction mixture was stirred at 25°C for 30 min. (2*R*)-2-aminopropanamide;hydrochloride (32.2 mg, 258.3 umol, 1.5 *eq*) was added to the mixture. The reaction mixture was stirred at 25°C for 3 hr. The residue was filtered, and the filtrate was obtained as brown liquid and purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100 * 40 mm * 5 um;mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-30%,8min) to give (*R*)-N-(1-amino-1-oxopropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00757] MS (ESI): *m/z* =361.1 $[M+H]^+$

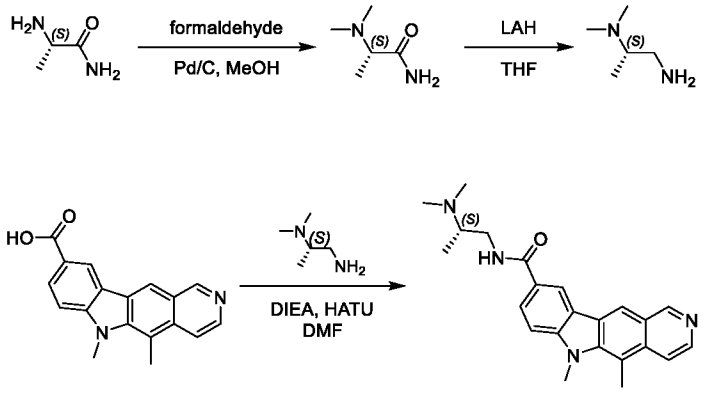
[00758] **N-(2-methoxy-2-methylpropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 299)**



[00759] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*) and HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred for 30 min. 2-methoxy-2-methylpropan-1-amine (21.3 mg, 206.6 umol, 1.2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 6 hr. The reaction mixture was concentrated to dryness. The crude product was purified by reversed-phase HPLC (TFA condition column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-40%,9min) to give N-(2-methoxy-2-methylpropyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00760] MS (ESI): *m/z* = 376.2 $[M+H]^+$

[00761] **(S)-N-(2-(dimethylamino)propyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 300)**



[00762] Step 1: (S)-2-(dimethylamino)propanamide

[00763] To a solution of (S)-2-aminopropanamide (1 g, 8.0 mmol, 1 *eq*, HCl) and formaldehyde (1.4 g, 17.6 mmol, 1.3 mL, 37% purity, 2.2 *eq*) in MeOH (15 mL) was added Pd/C (0.4 g, 10% purity). The mixture was stirred at 40°C for 5 hr under H_2 (15 psi). The mixture was filtered and concentrated under reduced pressure to give (S)-2-(dimethylamino)propanamide.

[00764] Step 2: (S)-N2,N2-dimethylpropane-1,2-diamine

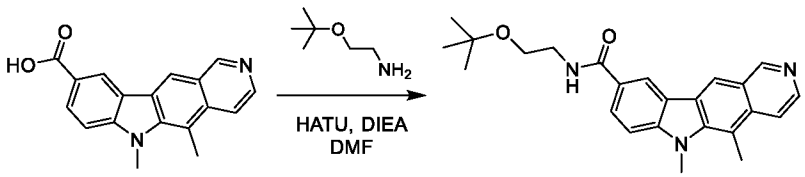
[00765] To a solution of (S)-2-(dimethylamino)propanamide (1.3 g, 8.5 mmol, 1 *eq*, HCl) in THF (20 mL) was added LAH (711.2 mg, 18.7 mmol, 2.2 *eq*). The mixture was stirred at 25°C for 1 hr. Then the mixture was stirred at 80°C for 12 hr under N_2. The reaction mixture was quenched by addition 0.7 mL Sat. $MgSO_4$, filtered and concentrated under reduced pressure to give (S)-N2,N2-dimethylpropane-1,2-diamine.

[00766] Step 3: (S)-N-(2-(dimethylamino)propyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide

[00767] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*), HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred for 30 min. (S)-N2,N2-dimethylpropane-1,2-diamine (35.2 mg, 344.4 umol, 2 *eq*) was added to the solution and stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove **solvent**. The residue was purified by prep-HPLC (**TFA condition,** column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-30%,8min) to give (S)-N-(2-(dimethylamino)propyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00768] MS (ESI): *m/z* = 375.2 $[M+H]^+$

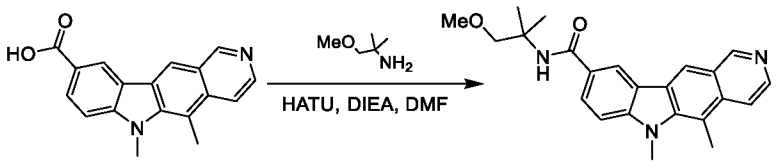
[00769] **N-(2-(tert-butoxy)ethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide (Compound 301)**



[00770] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxylic acid (50 mg, 172.2 umol, 1 *eq*) in DMF (2 mL) was added DIEA (66.7 mg, 516.6 umol, 90.0 uL, 3 *eq*), HATU (98.2 mg, 258.3 umol, 1.5 *eq*) and stirred at 25°C for 30 min. 2-tert-butoxyethanamine;hydrochloride (52.9 mg, 344.4 umol, 2 *eq*) was added to the solution and stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove **solvent.** The residue was purified by prep-HPLC (**TFA condition,** column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%,8min) to give N-(2-(tert-butoxy)ethyl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carboxamide.

[00771] MS (ESI): *m/z* = 390.2 $[M+H]^+$

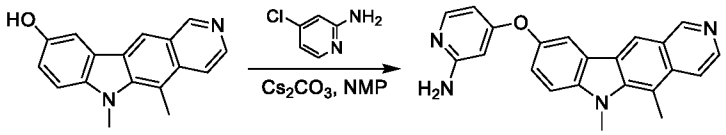
[00772] **N-(1-methoxy-2-methylpropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carb-oxamide (Compound 302)**



[00773] To a solution of 5,6-dimethylpyrido[4,3-b]carbazole-9-carboxylic acid (80 mg, 275.6 umol, 1 *eq*) in DMF (2 mL) was added DIEA (106.8 mg, 826.7 umol, 143.9 uL, 3 *eq*) and HATU (157.2 mg, 413.3 umol, 1.5 *eq*). The reaction mixture was stirred at 25°C for 30 min. 1-Methoxy-2-methyl-propan-2-amine (42.6 mg, 413.3 umol, 1.5 *eq*) was added to the mixture. The reaction mixture was stirred at 25°C for 3 hr. The residue was filtered, and the filtrate was obtained as brown liquid and purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-36%, 8min) to give N-(1-methoxy-2-methylpropan-2-yl)-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-9-carb-oxamide.

[00774] MS (ESI): *m/z* =376.2 $[M+H]^+$

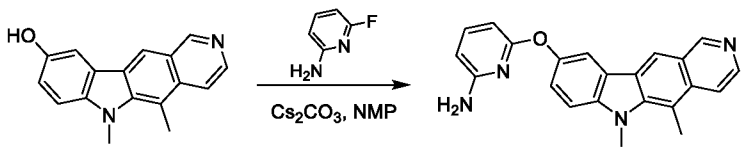
[00775] **4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridin-2-amine (Compound 303)**



[00776] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 *eq*) in NMP (3 mL) was added 4-chloropyridin-2-amine (58.8 mg, 457.4 umol, 1.2 *eq*) and Cs_2CO_3 (149.0 mg, 457.4 umol, 1.2 *eq*). The mixture was stirred at 220°C for 1 hr under microwave. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-40%,8min) to give 4-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridin-2-amine.

[00777] MS (ESI): *m/z* = 355.1 $[M+H]^+$

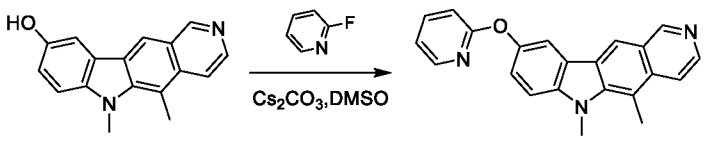
[00778] **6-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridin-2-amine (Compound 304)**



[00779] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 *eq*) in NMP (3 mL) was added 6-fluoropyridin-2-amine (51.2 mg, 457.4 umol, 1.2 *eq*) and Cs_2CO_3 (149.0 mg, 457.4 umol, 1.2 *eq*). The mixture was stirred at 220°C for 1 hr under microwave. The reaction mixture was filtered, and the filtrate dried in vacuum to give crude product. The residue was purified by prep-HPLC (basic condition, column: Phenomenex Gemini-NX C18 75*30mm*3um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give 6-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridin-2-amine.

[00780] MS (ESI): *m/z* = 355.1 $[M+H]^+$

[00781] **5,6-dimethyl-9-(pyridin-2-yloxy)-6H-pyrido[4,3-b]carbazole (Compound 305)**

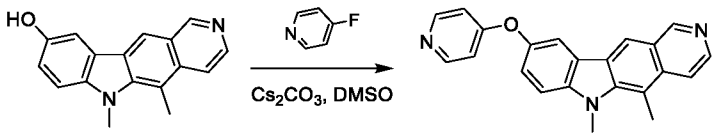


[00782] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (70 mg, 266.8 umol, 1 *eq*) in DMSO (1 mL) was added 2-fluoropyridine (31.0 mg, 320.2 umol, 27.5 uL, 1.2 *eq*) and Cs_2CO_3 (260.8 mg, 800.5 umol, 3 *eq*). The mixture was stirred at 120°C for 12 hr. The reaction mixture was concentrated to dryness. The residue was purified by prep-HPLC

(0.05% $NH_3•H_2O$ column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [water(0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN];B%: 35%-65%,8min) to give 5,6-dimethyl-9-(pyridin-2-yloxy)-6H-pyrido[4,3-b]carbazole.

[00783] MS (ESI): *m/z* = 340.1 $[M+H]^+$

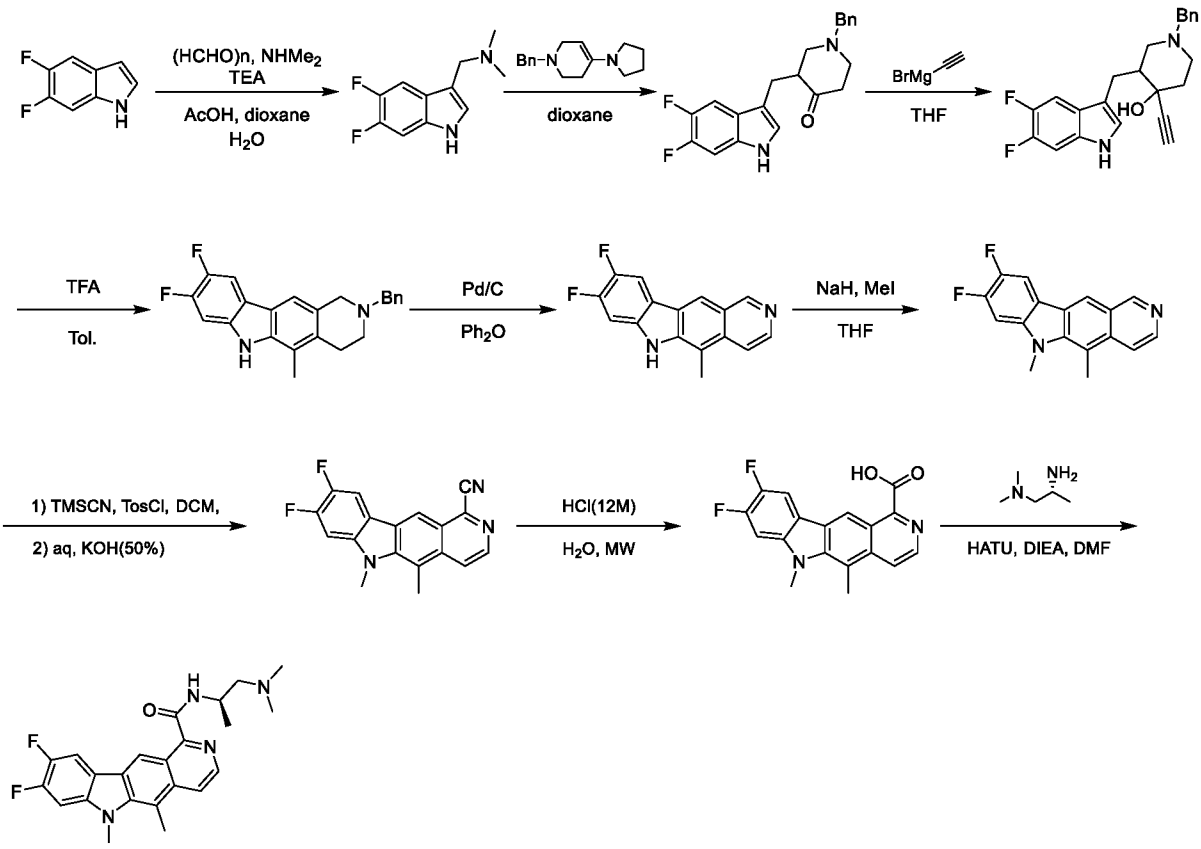
[00784] **5,6-dimethyl-9-(pyridin-4-yloxy)-6H-pyrido[4,3-b]carbazole (Compound 306)**



[00785] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (60 mg, 228.7 umol, 1 *eq*) in DMSO (2 mL) was added 4-fluoropyridine (36.6 mg, 274.4 umol, 1.2 *eq*, HCl) and Cs_2CO_3 (223.5 mg, 686.2 umol, 3*eq*). The mixture was stirred at 120 °C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-30%,9min) to give 5,6-dimethyl-9-(pyridin-4-yloxy)-6H-pyrido[4,3-b]carbazole.

[00786] MS (ESI): *m/z* = 340.1 $[M+H]^+$

[00787] **(R)-N-(1-(dimethylamino)propan-2-yl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 307)**



[00788] Step 1: 1-(5,6-difluoro-1H-indol-3-yl)-N,N-dimethylmethanamine

[00789] To a solution of 5,6-difluoro-1H-indole (5 g, 32.6 mmol, 1 *eq*) in dioxane (56 mL) and H_2O (56 mL) was added dimethylamine hydrochloride (2.9 g, 35.9 mmol, 1.1 *eq*), formaldehyde (2.9 g, 35.9 mmol, 2.6 mL, 37% purity, 1.1 *eq*), TEA (3.6 g, 35.9 mmol, 5.0 mL, 1.1 *eq*), AcOH (2.9 g, 48.9 mmol, 2.8 mL, 1.5 *eq*). The mixture was stirred at 30°C for 12 hr. The mixture was concentrated to remove the dioxane and poured into NaOH (200 mL, 2N). The precipitate was collected by filtration and washed with H_2O (300 mL) to give 1-(5,6-difluoro-1H-indol-3-yl)-N,N-dimethylmethanamine.

[00790] Step 2: 1-benzyl-3-((5,6-difluoro-1H-indol-3-yl)methyl)piperidin-4-one

[00791] To a solution of 1-(5,6-difluoro-1H-indol-3-yl)-N,N-dimethylmethanamine (6 g, 28.5 mmol, 1 *eq*) in dioxane (70 mL) was added 1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine (17.2 g, 71.3 mmol, 2.5 *eq*). The mixture was stirred at 120°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 120 mL/min) to give 1-benzyl-3-[(5,6-difluoro-1H-indol-3-yl)methyl]piperidin-4-one.

[00792] Step 3: 1-benzyl-3-((5,6-difluoro-1H-indol-3-yl)methyl)-4-ethynylpiperidin-4-ol

[00793] To a solution of 1-benzyl-3-[(5,6-difluoro-1H-indol-3-yl)methyl]piperidin-4-one (5.2 g, 14.6 mmol, 1 *eq*) in THF (40 mL) was added bromo(ethynyl)magnesium (0.5 M, 117.3 mL, 4 *eq*) at 0°C. The mixture was stirred at 0°C for 1 hr. The reaction mixture was quenched by addition NH_4Cl (200 mL) at 25°C, and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL × 3), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-benzyl-3-((5,6-difluoro-1H-indol-3-yl)methyl)-4-ethynylpiperidin-4-ol.

[00794] Step 4: 2-benzyl-8,9-difluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00795] To a solution of 1-benzyl-3-[(5,6-difluoro-1H-indol-3-yl)methyl]-4-ethynylpiperidin-4-ol (6 g, 15.7 mmol, 1 *eq*) in Tol. (117 mL) was added TFA (17.9 g, 157.7 mmol, 11.6 mL, 10 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was partitioned between $NaHCO_3$ 300 mL and EtOAc 300 mL. The water phase was separated, extracted with EtOAc (300 mL × 3). The combined organic phase was washed with brine (300 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 120mL/min) to give 2-benzyl-8,9-difluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

[00796] Step5: 8,9-difluoro-5-methyl-6H-pyrido[4,3-b]carbazole

[00797] To a solution of 2-benzyl-8,9-difluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (4 g, 11.0 mmol, 1 *eq*) in Ph_2O (50 mL) was added Pd/C (2 g, 10% purity). The mixture was stirred at 220°C for 4 hr. The reaction mixture was filtered and washed with the solvent (DCM : MeOH = 10:1) （300 mL × 3） and the filtrate was dried in vacuum to give crude product. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 120 mL/min) to give 8,9-difluoro-5-methyl-6H-pyrido[4,3-b]carbazole.

[00798] Step 6: 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00799] To a solution of 8,9-difluoro-5-methyl-6H-pyrido[4,3-b]carbazole (2.9 g, 11.0 mmol, 1 *eq*) in THF (30 mL) was added NaH (1.3 g, 33.1 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. Then MeI (1.5 g, 11.0 mmol, 686.9 uL, 1 *eq*) was added to the mixture and stirred at 25°C for 2 hr. The residue was diluted with NH_4Cl 200 mL and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (200 mL × 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 25 g SepaFlash® Silica

Flash Column, Eluent of 0~10% MeOH/CH_2Cl_2@ 120 mL/min) to give 8,9-difluoro-5,6-dimethyl-pyrido[4,3-b]carbazole.

[00800] Step 7: 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00801] To a solution of 8,9-difluoro-5,6-dimethyl-pyrido[4,3-b]carbazole (600 mg, 2.1 mmol, 1 *eq*) in DCM (10 mL) was added trimethylsilylcyanide (548.2 mg, 5.5 mmol, 691.3 uL, 2.6 *eq*). A solution of TosCl (769.9 mg, 4.0 mmol, 1.9 *eq*) in DCM (5 mL) was added to the mixture at 25°C. Then the mixture was stirred at 30°C for 12 hr. Then, 10 mL KOH (50% W/W) was added to the reaction. The mixture was stirred at 30°C for 2 hr. The reaction mixture was filtered, and the filter cake was washed with 20 mL of H_2O, dried in vacuum to give 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

[00802] Step 8: 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

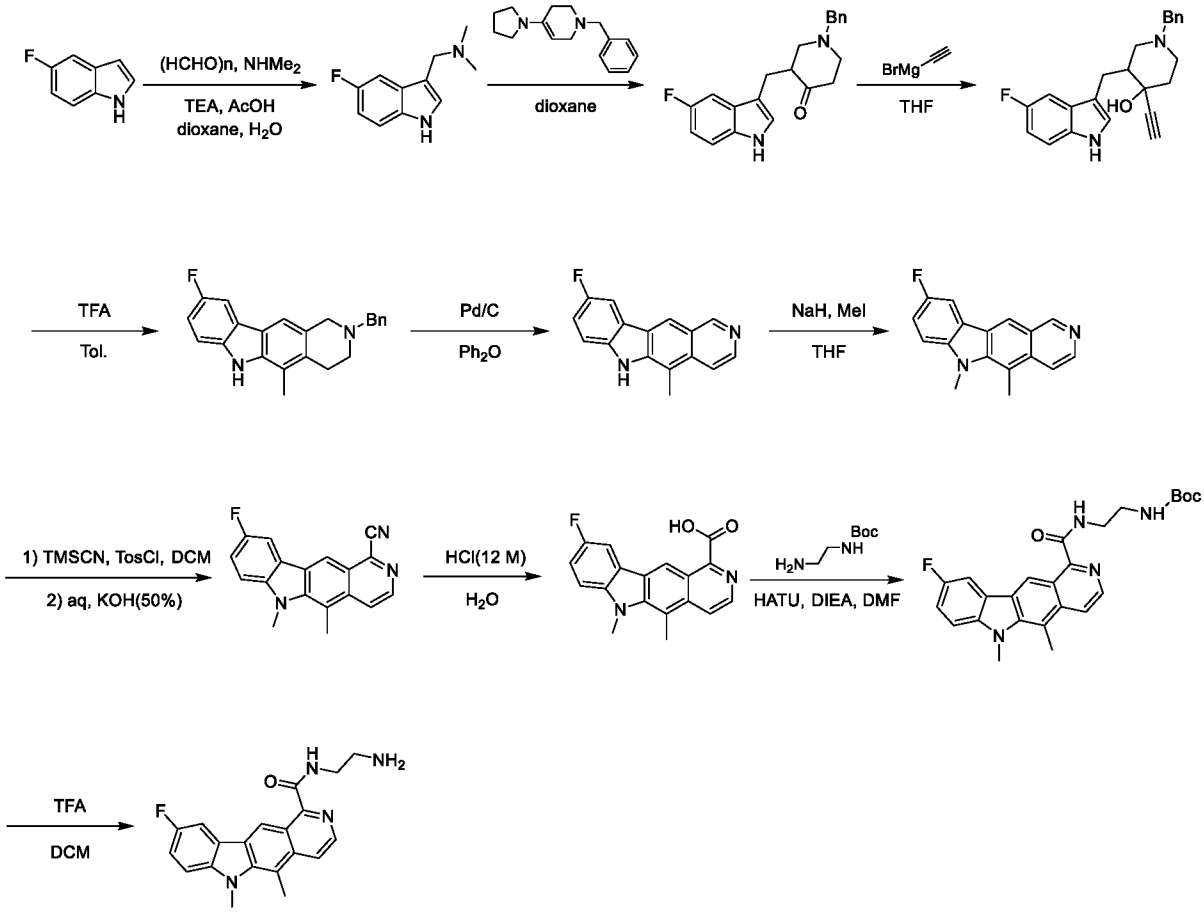
[00803] A mixture of 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (100 mg, 325.4 umol, 1 *eq*) in HCl (2 mL) (12 M) was stirred at 130°C for 4 hr under microwave. The reaction mixture was added to $NaHCO_3$ (10 mL) and filtered, and the filter cake was washed with 10 mL of H_2O, dried in vacuum to give 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

[00804] Step 9: (R)-N-(1-(dimethylamino)propan-2-yl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00805] To a solution of 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (30 mg, 91.9 umol, 1 *eq*) in DMF (1 mL) was added DIEA (35.6 mg, 275.8 umol, 48.0 uL, 3 *eq*) and HATU (52.4 mg, 137.9 umol, 1.5 *eq*) and stirred for 30 min. (2R)-N1,N1-dimethylpropane-1,2-diamine (32.2 mg, 183.8 umol, 2 *eq*, 2 HCl) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was filtered, and the filtrate dried in vacuum to give crude product. The residue was purified by prep-HPLC (**TFA condition, co**lumn: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 15%-45%,9min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00806] MS (ESI): *m/z* = 411.2 $[M+H]^+$

[00807] **N-(2-aminoethyl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 308)**



[00808] Step 1: 1-(5-fluoro-1H-indol-3-yl)-N,N-dimethylmethanamine

[00809] To a solution of 5-fluoro-1H-indole (20 g, 148.0 mmol, 1 *eq*) in dioxane (283 mL) and H_2O (283 mL) was added dimethylamine hydrochloride (13.2 g, 162.8 mmol, 1.1 *eq*), formaldehyde (13.2 g, 162.8 mmol, 12.1 mL, 37% purity, 1.1 *eq*), TEA (16.4 g, 162.8 mmol, 22.6 mL, 1.1 *eq*) and AcOH (13.3 g, 222.0 mmol, 12.7 mL, 1.5 *eq*). The mixture was stirred at 30°C for 12 hr. The mixture was concentrated to remove the dioxane and poured into NaOH (1000 mL, 2 N) and white solid was separated out. The mixture was filtered and wash with H_2O (500 mL) to give 1-(5-fluoro-1H-indol-3-yl)-N,N-dimethylmethanamine.

[00810] Step 2: 1-benzyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-one

[00811] To a solution of 1-(5-fluoro-1H-indol-3-yl)-N,N-dimethylmethanamine (15 g, 78.0 mmol, 1 *eq*) in dioxane (120 mL) was added 1-benzyl-4-(pyrrolidin-1-yl)-1,2,3,6-tetrahydropyridine (47.2 g, 195.0 mmol, 2.5 *eq*). The mixture was stirred at 120°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient @ 100 mL/min) to give 1-benzyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-one.

[00812] Step 3: 1-benzyl-4-ethynyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-ol

[00813] To a solution of 1-benzyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-one (2 g, 5.9 mmol, 1 *eq*) in THF (15 mL) was added bromo(ethynyl)magnesium (0.5 M, 47.5 mL, 4 *eq*) at 0°C. The mixture was stirred at 0°C for 1 hr. The reaction mixture was quenched by addition NH_4Cl (50 mL) at 25°C, and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (50 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-benzyl-4-ethynyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-ol.

[00814] Step 4: 2-benzyl-9-fluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole

[00815] To a solution of 1-benzyl-4-ethynyl-3-((5-fluoro-1H-indol-3-yl)methyl)piperidin-4-ol (2 g, 5.5 mmol, 1 *eq*) in Tol. (40 mL) was added TFA (6.2 g, 55.1 mmol, 4.0 mL, 10 *eq*). The mixture was stirred at 80°C for 12 hr. The reaction mixture was partitioned between $NaHCO_3$ 100 mL and EtOAc 100 mL. The water phase was separated, extracted with EtOAc (100 mL × 3). The combined organic phase was washed with brine (100 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 80mL/min) to give 2-benzyl-9-fluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole.

[00816] Step 5: 9-fluoro-5-methyl-6H-pyrido[4,3-b]carbazole

[00817] To a solution of 2-benzyl-9-fluoro-5-methyl-2,3,4,6-tetrahydro-1H-pyrido[4,3-b]carbazole (1 g, 2.9 mmol, 1 *eq*) in Ph_2O (10 mL) was added Pd/C (1 g, 10% purity). The mixture was stirred at 220°C for 4 hr. The reaction mixture was filtered and washed with the solvent (DCM : MeOH = 10:1) （100 mL × 3） and the filtrate was dried in vacuum to give crude product. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~10% MeOH/DCM@ 80 mL/min) to give 9-fluoro-5-methyl-6H-pyrido[4,3-b]carbazole.

[00818] Step 6: 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole

[00819] To a solution of 9-fluoro-5-methyl-6H-pyrido[4,3-b]carbazole (320 mg, 1.2 mmol, 1 *eq*) in THF (10 mL) was added NaH (153.4 mg, 3.8 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. Then MeI (181.4 mg, 1.2 mmol, 79.6 uL, 1 *eq*) was added to mixture and stirred at 25°C for 2 hr. TLC indicated one new spot formed. The residue was diluted with NH_4Cl 50 mL and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole as a yellow solid.

[00820] Step 7: 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile

[00821] To a mixture of 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (430 mg, 1.6 mmol, 1 *eq*) in DCM (10 mL) was added trimethylsilylcyanide (419.6 mg, 4.2 mmol, 529.2 uL, 2.6 *eq*). To this mixture a solution of TosCl (589.3 mg, 3.0 mmol, 1.9 *eq*) in DCM (2 mL) was added at 25°C. Then the mixture was stirred at 30°C for 12 hr. LCMS showed the intermediate was detected and 10 mL KOH (50% W/W) was added to the reaction. The mixture was stirred at 30°C for 2 hr. The reaction mixture was diluted with H_2O 20 mL and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine (10 mL × 2), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile.

[00822] Step 8: 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid

[00823] The solution of 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carbonitrile (140 mg, 483.9 umol, 1 *eq*) in HCl (5 mL) (12 M) was stirred at 130°C for 4 hr. The reaction mixture was diluted with $NaHCO_3$ 15 mL, filtered and concentrated under reduced pressure to give 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid.

[00824] Step 9: tert-butyl (2-(9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate

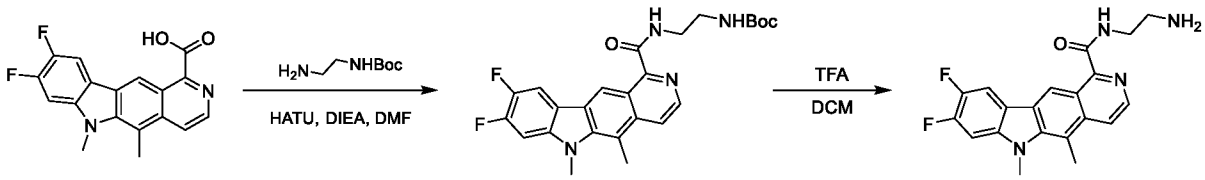
[00825] To a solution of 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (60 mg, 194.6 umol, 1 *eq*) in DMF (2 mL) was added DIEA (75.4 mg, 583.8 umol, 101.6 uL, 3 *eq*) and HATU (111.0 mg, 291.9 umol, 1.5 *eq*) at 25°C, then the reaction was stirred at 25°C for 30 min. tert-butyl N-(2-aminoethyl)carbamate (62.3 mg, 389.2 umol, 61.1 uL, 2 *eq*) was added to the mixture and stirred at 25°C for 12 hr. The reaction mixture was diluted with H_2O 5 mL and the product was precipitated out, the filtrate cake was concentrated under reduced pressure to give tert-butyl (2-(9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate.

[00826] Step 10: N-(2-aminoethyl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00827] To a solution of tert-butyl (2-(9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1- carboxamido)ethyl)carbamate (60 mg, 133.1 umol, 1 *eq*) in DCM (2 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL, 101.4 *eq*). The mixture was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 20%-50%,8min) to give N-(2-aminoethyl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00828] MS (ESI): *m/z* = 351.1 $[M+H]^+$

[00829] **N-(2-aminoethyl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 309)**



[00830] Step 1: tert-butyl (2-(8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate

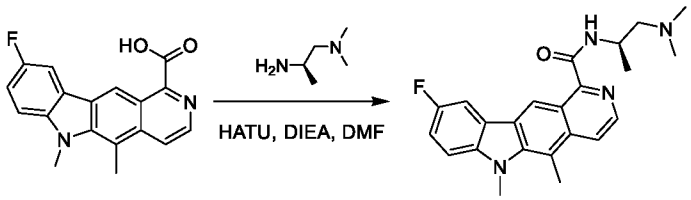
[00831] To a solution of 8,9-difluoro-5,6-dimethyl-pyrido[4,3-b]carbazole-1-carboxylic acid (100 mg, 306.4 umol, 1 *eq*) in DMF (3 mL) was added DIEA (118.8 mg, 919.4 umol, 160.1 uL, 3 *eq*), HATU (174.7 mg, 459.7 umol, 1.5 *eq*) and stirred for 30 min. tert-butyl N-(2-aminoethyl)carbamate (98.2 mg, 612.9 umol, 96.2 uL, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The reaction mixture was added to H_2O (3 mL) and filtered, and the filter cake was washed with 2 mL of H_2O, dried in vacuum to give tert-butyl (2-(8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate.

[00832] Step 2: N-(2-aminoethyl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide

[00833] A mixture of tert-butyl (2-(8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamido)ethyl)carbamate(90 mg, 192.1 umol, 1 *eq*) in TFA (1 mL) and DCM (2 mL) was stirred at 25°C for 1 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition,column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 20%-50%,8min) to give N-(2-aminoethyl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00834] MS (ESI): *m/z* = 369.1 $[M+H]^+$

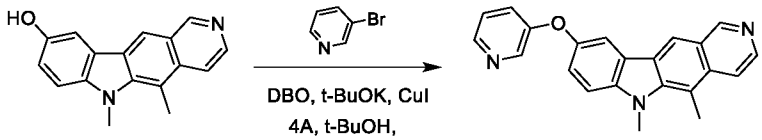
[00835] **(R)-N-(1-(dimethylamino)propan-2-yl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 310)**



[00836] To a solution of 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (50 mg, 162.1 umol, 1 *eq*) in DMF (2 mL) was added DIEA (62.8 mg, 486.5 umol, 84.7 uL, 3 *eq*) and HATU (92.5 mg, 243.2 umol, 1.5 *eq*) at 25°C, then the reaction was stirred at 25°C for 30 min. (2R)-N1,N1-dimethylpropane-1,2-diamine (56.7 mg, 324.3 umol, 2 *eq*, 2 HCl) was added to the mixture and stirred at 25°C for 12 hr. (2R)-N1, N1-dimethylpropane-1, 2-diamine (14.2 mg, 81.0 umol, 0.5 *eq*, 2 HCl) was added to the reaction and stirred at 25°C for 2 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 100*30mm*5um;mobile phase: [water(0.1%TFA)-MeOH];B%: 30%-60%,10min) to give (R)-N-(1-(dimethylamino)propan-2-yl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00837] MS (ESI): *m/z* = 393.2 $[M+H]^+$

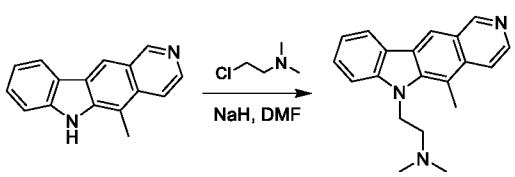
[00838] **5,6-dimethyl-9-(pyridin-3-yloxy)-6H-pyrido[4,3-b]carbazole (Compound 311)**



[00839] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (199.2 mg, 759.5 umol, 1.2 *eq*) in t-BuOH (2 mL) was added 3-bromopyridine (100 mg, 632.9 umol, 60.9 uL, 1 *eq*), CuI (1.2 mg, 6.3 umol, 0.01 *eq*), N,N□-dibenzyloxamide (3.4 mg, 12.7 umol, 0.02 *eq*), t-BuOK (142.0 mg, 1.2 mmol, 2 *eq*) and 4A molecular sieve (300 mg) under N_2. The reaction mixture was stirred at 100°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent and diluted with dimethyl sulfoxide (2 mL). The residue was purified by prep-HPLC (TFA condition; column: Waters Xbridge BEH C18 100*25mm*5um;mobile phase: [water(10mM NH_4HCO_3)-ACN];B%: 35%-65%,10min) to give 5,6-dimethyl-9-(pyridin-3-yloxy) -6H-pyrido[4,3-b]carbazole.

[00840] MS (ESI): *m/z* = 340.1 $[M+H]^+$

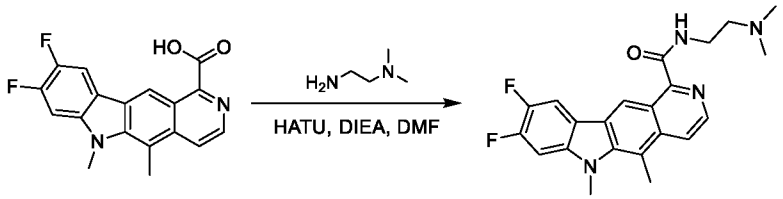
[00841] **N,N-dimethyl-2-(5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethanamine (Compound 312)**



[00842] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazole (80 mg, 344.4 umol, 1 *eq*) in DMF (2 mL) was added NaH (41.3 mg, 1.0 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. 2-chloro-N,N-dimethyl-ethanamine (59.5 mg, 413.3 umol, 1.2 *eq*, HCl) was added to the mixture and stirred at 25°C for 12 hr. The reaction was stirred at 70°C for 12 hr. The reaction mixture was diluted with FA 1 mL, and then filtered and the filtrate was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-25%,8min) to give N,N-dimethyl-2-(5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethanamine.

[00843] MS (ESI): *m/z* = 304.1 $[M+H]^+$

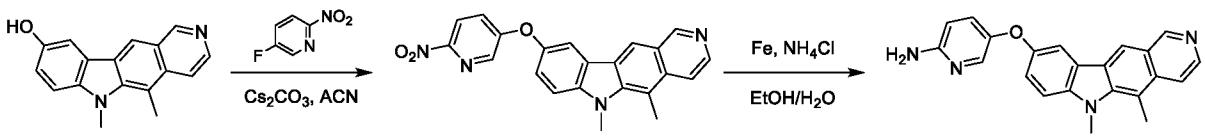
[00844] **N-(2-(dimethylamino)ethyl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 313)**



[00845] To a solution of 8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (80 mg, 245.1 umol, 1 *eq*) in DMF (2 mL) was added DIEA (95.0 mg, 735.5 umol, 128.1 uL, 3 *eq*) and HATU (139.8 mg, 367.7 umol, 1.5 *eq*) at 25°C, then the reaction was stirred at 25°C for 30 min. N,N-dimethylethane-1,2-diamine (43.2 mg, 490.3 umol, 53.5 uL, 2 *eq*) was added to the mixture and stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 10%-45%,8min) to give N-(2-(dimethylamino)ethyl)-8,9-difluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00846] MS (ESI): *m/z* = 397.1 $[M+H]^+$

[00847] **5-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridine -2-amine (Compound 314)**



[00848] Step 1: 5,6-dimethyl-9-((6-nitropyridin-3-yl)oxy)-6H-pyrido[4,3-b]carbazole

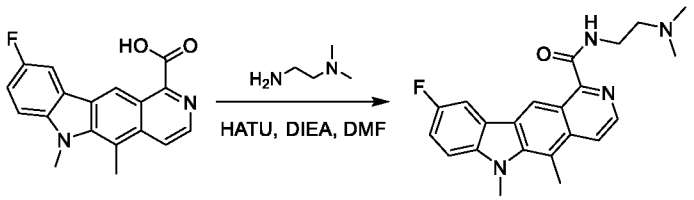
[00849] To a solution of 5,6-dimethylpyrido[4,3-b]carbazol-9-ol (221.5 mg, 844.5 umol, 1.2 *eq*) in ACN (2 mL) was added 5-fluoro-2-nitro-pyridine (100 mg, 703.7 umol, 12.2 uL, 1 *eq*) and Cs_2CO_3 (458.6 mg, 1.4 mmol, 2. *eq*) under N_2. The reaction mixture was stirred at 80°C for 12 hr. The reaction mixture was concentrated filtered. The filter cake was washed with H_2O (50 mL) and concentrated under reduced pressure to give 5,6-dimethyl-9-((6-nitropyridin-3-yl)oxy)-6H-pyrido[4,3-b]carbazole.

[00850] Step 2: 5-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridin-2-amine

[00851] To a solution of 5,6-dimethyl-9-[(6-nitro-3-pyridyl)oxy]pyrido[4,3-b]carbazole (200 mg, 520.3 umol, 1 *eq*) in EtOH (4 mL) / H_2O (1 mL) was added Fe (145.2 mg, 2.6 mmol, 5 *eq*) and NH_4Cl (139.1 mg, 2.6 mmol, 5 *eq*). The reaction mixture was stirred at 80°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with DMF (2 mL) and DMSO (2 mL). The residue was purified by prep-HPLC (TFA condition;column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 3%-38%,8min) to give 5-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)pyridine -2-amine.

[00852] MS (ESI): *m/z* = 355.1 $[M+H]^+$

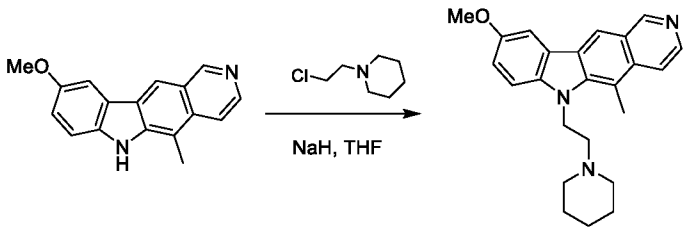
[00853] **N-(2-(dimethylamino)ethyl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide (Compound 315)**



[00854] To a solution of 9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxylic acid (80 mg, 259.4 umol, 1 *eq*) in DMF (2 mL) was added DIEA (100.6 mg, 778.4 umol, 135.5 uL, 3 *eq*) and HATU (147.9 mg, 389.2 umol, 1.5 *eq*) at 25°C, then the reaction was stirred at 25°C for 30 min. N,N-dimethylethane-1,2-diamine (45.7 mg, 518.9 umol, 56.6 uL, 2 *eq*) was added to the mixture and stirred at 25°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-50%,8min) to give N-(2-(dimethylamino)ethyl)-9-fluoro-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide.

[00855] MS (ESI): *m/z* = 379.1 $[M+H]^+$

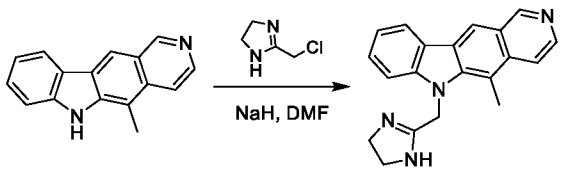
[00856] **9-methoxy-5-methyl-6-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole (Compound 316)**



[00857] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (100 mg, 381.2 umol, 1 *eq*) in DMF (2 mL) was added NaH (45.7 mg, 1.1 mmol, 60% purity, 3 *eq*) at 0°C. The reaction mixture was stirred at 0°C for 30 min. 1-(2-chloroethyl)piperidine (112.6 mg, 611.5 umol, 1.6 *eq*, HCl) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The pH of reaction mixture was adjusted to 7 by addition of formic acid. The reaction mixture was filtered. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30 mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 10%-40%, 8 min) to give 9-methoxy-5-methyl-6-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole.

[00858] MS (ESI): *m/z* = 374.1 $[M+H]^+$

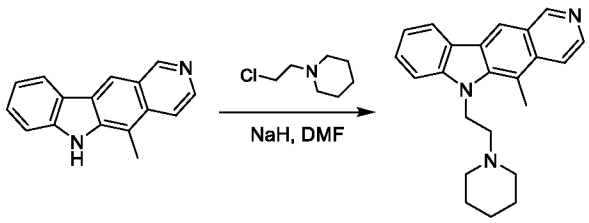
[00859] **6-((4,5-dihydro-1H-imidazol-2-yl)methyl)-5-methyl-6H-pyrido[4,3-b]carbazole (Compound 317)**



[00860] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazole (80 mg, 344.4 umol, 1 *eq*) in DMF (2 mL) was added NaH (68.8 mg, 1.7 mmol, 60% purity, 5 *eq*) and 2-(chloromethyl)-4,5-dihydro-1H-imidazole (106.7 mg, 688.8 umol, 2 *eq*, HCl). The mixture was stirred at 70°C for 2 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex Luna 80*30mm*3um;mobile phase: [water(0.1%TFA)-ACN];B%: 5%-35%,8min) to give 6-((4,5-dihydro-1H-imidazol-2-yl)methyl)-5-methyl-6H-pyrido[4,3-b]carbazole.

[00861] MS (ESI): *m/z* = 315.1 $[M+H]^+$

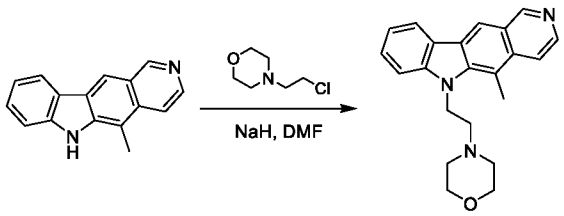
[00862] **5-methyl-6-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole (Compound 318)**



[00863] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazole (50 mg, 215.2 umol, 1 *eq*) in DMF (2 mL) was added NaH (25.8 mg, 645.7 umol, 60% purity, 3 *eq*). The mixture was stirred at 25°C for 10 min. 1-(2-chloroethyl)piperidine (63.5 mg, 430.5 umol, 2 *eq*) was added to the mixture. The mixture was stirred at 25°C for 2 hr. The reaction mixture was partitioned between NH_4Cl 5 mL and EtOAc 5 mL. The water phase was separated, extracted with EtOAc (5 mL × 3). The combined organic phase was washed with brine (5 mL × 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition; column: Phenomenex Luna C18 150*30mm*5um;mobile phase: [water(0.2%FA)-ACN];B%: 2%-30%,8min) to give 5-methyl-6-(2-(piperidin-1-yl)ethyl)-6H-pyrido[4,3-b]carbazole.

[00864] MS (ESI): *m/z* = 344.1 $[M+H]^+$

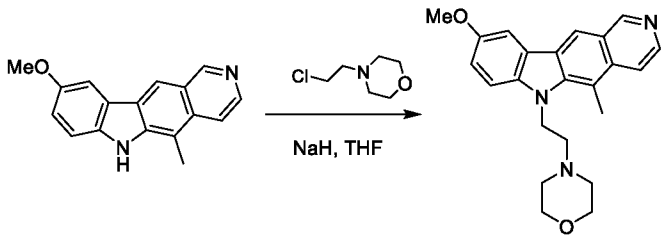
[00865] **4-(2-(5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethyl)morpholine (Compound 319)**



[00866] To a solution of 5-methyl-6H-pyrido[4,3-b]carbazole (80 mg, 344.4 umol, 1 *eq*) in DMF (2 mL) was added NaH (41.3 mg, 1.0 mmol, 60% purity, 3 *eq*) at 0°C and stirred for 30 min. 4-(2-chloroethyl)morpholine (128.1 mg, 688.8 umol, 2 *eq*, HCl) was added to the mixture. The mixture was stirred at 25°C for 12 hr. The mixture was stirred at 70°C for 12 hr. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition, column: Phenomenex luna C18 100*40mm*5 um;mobile phase: [water(0.1%TFA)-ACN];B%: 1%-20%,8min) to give 4-(2-(5-methyl-6H-pyrido[4,3-b] carbazol-6-yl)ethyl)morpholine.

[00867] MS (ESI): *m/z* =346.1$[M+H]^+$

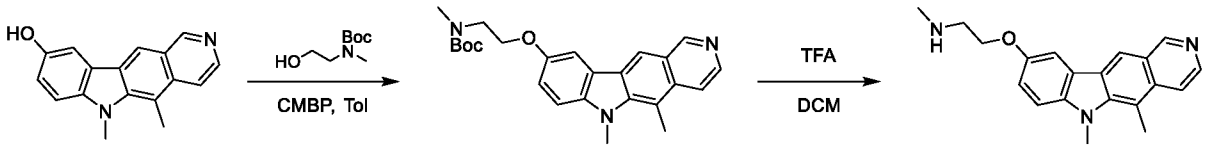
[00868] **4-(2-(9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethyl)morpholine (Compound 320)**



[00869] To a solution of 9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazole (100 mg, 381.2 umol, 1 *eq*) in DMF (2 mL) was added NaH (45.7 mg, 1.1 mmol, 60% purity, 3 *eq*) at 0°C. The reaction mixture was stirred at 0°C for 30 min. 4-(2-chloroethyl)morpholine (113.8 mg, 611.5 umol, 1.6 *eq*, HCl) was Added to the mixture. The reaction mixture was stirred at 25°C for 12 hr. The pH of reaction mixture was adjusted to 7 by addition formic acid. The reaction mixture was filtered. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex Luna C18 150*30mm*5 um; mobile phase: [water(0.1%TFA)-ACN];B%: 10%-40%, 8 min) to give 4-(2-(9-methoxy-5-methyl-6H-pyrido[4,3-b]carbazol-6-yl)ethyl)morpholine.

[00870] MS (ESI): *m/z* = 376.1 $[M+H]^+$

[00871] **2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylethanamine (Compound 321)**



[00872] Step 1: tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)(methyl)carbamate

[00873] To a solution of 5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-ol (100 mg, 381.2 umol, 1 *eq*) in toluene (3 mL) was added tert-butyl N-(2-hydroxyethyl)-N-methyl-carbamate (66.8 mg, 381.24 umol, 1 *eq*) and 2-(tributyl-λ^5-phosphanylidene)acetonitrile (9.2 mg, 38.1 umol, 0.1 *eq*). The reaction mixture was stirred at 100°C for 12 hr. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with (DCM 2 mL). The residue was purified by prep-TLC (SiO2, DCM: MeOH = 10:1) to give tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)(methyl)carbamate.

[00874] Step 2; 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylethanamine

[00875] To a solution of tert-butyl (2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)ethyl)(methyl)carbamate (100 mg, 238.4 umol, 1 *eq*) in DCM (2 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL, 56.7 *eq*). The reaction mixture was stirred at 25°C for 12 hr. The

reaction mixture was diluted with methanol (2mL) and filtered. The residue was purified by prep-HPLC (TFA condition; column: Phenomenex luna C18 100*40 mm*5 um; mobile phase: [water(0.1%TFA)-ACN]; B%: 1%-35%, 8 min) to give 2-((5,6-dimethyl-6H-pyrido[4,3-b]carbazol-9-yl)oxy)-N-methylethanamine.

[00876] MS (ESI): *m/z* = 320.1 $[M+H]^+$

[00877] Other compounds disclosed herein can be synthesized similarly as described in the above examples.

[00878] **Inhibition assay of compounds.** The IC_{50} values for inhibition of RNA translation for Compounds 1-84, 202-257, and 262-321 were measured. Data are presented in Tables D, E, F, and G below. These experiments were completed by co-transfecting HEK293T cells with *$(G_4C_2)_{66}$-No ATG-GFP* (SEQ ID NO: 11) and a plasmid encoding containing mCherry (*ATG-mCherry*). The transfected cells were then treated with varying amounts of compound and the percent inhibition of RAN translation was comparing the GFP signal in treated cells to cells treated with vehicle. Percent inhibition was plotted as a function of compound concentration and the resulting curve was fit to a four-parameter logistic curve fit (Sigma Plot).

[00879] The BLI K_d data in Table G below was obtained using the below procedure. Biotin-labeled RNA was incubated with test compounds in a streptavidin-labeled biosensor from ForteBio. Affinity of the test compounds for the target RNA was measured in a ForteBio Octet RED384 BLI system.

Table D

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
1	>200	>5
2	>200	--
3	8.3	0.1
4a	4.5	0.9
4b	>200	--
5	20	0.5
6	32	>5
7	12	>5
8	11	0.36

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
9	10	0.27
10	7.3	3.2
11	16	0.4
12	18	0.3
13	>200	--
14	>200	--
15	>200	--
16	>200	--
17	>200	--

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
18	>200	--
19	>200	--
20	>200	--
21	>200	--
22	>200	--
23	9.4	>5
24	>200	--
25	39	0.27
26	5.9	0.57
27	9.1	1.0
28	8.1	0.64
29	17	0.74
30	2.5	2.2
31	4.5	2.8
32	9.5	1.4
33	5.2	3.7
34	6.1	1.2
35	38	>5
36	3.9	>5
37	0.84	2.3
38	0.76	0.74
39	0.80	1.3
40	>200	--
41	0.6	0.67
42	9.2	>5
43	27	--

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
44a	10	--
44b	>200	--
45	21	--
46	4.6	--
47	>200	---
48	>200	---
49	>200	---
50	33	0.27
51	6.0	>5
52	5.6	3.1
53	>200	--
54	13	1.3
55	1.5	0.92
56	1.0	0.67
57	5.2	4.0
58	1.0	--
59	1.3	--
60	3.8	>5
61	0.90	1.0
62	>200	>5
63	1.8	4.8
64	>200	>5
65	4.2	--
66	>200	--
67	>200	--
68	4.0	0.72

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
69	12	1.6
70	36	3.6
71	107	>5
72	15	>5
73	13	0.84
74	2.5	>5
75	29	1.4
76	4.2	2.2
77	1.2	1.7

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
78	3.6	1.6
79	12	1.1
80a	30	>5
80b	9.2	3.1
81	>200	--
82	20	>5
83	2.3	1.1
84	13	>5

Table E

ID No.	IC_{50} (μM)
202	12
203	>12.5
204	12.5
205	12.5
206	>12.5
207	6

ID No.	IC_{50} (μM)
208	2.2
209	3.1
210	10.3
211	3.1
212	3.1

Table F

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
213	1.2	1.7
214	3.6	1.0
215	12	>5
216	6.9	1.7
217	8.5	>5
218	0.80	0.84

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
219	1.2	>5
220	2.3	>5
221	0.7	0.66
222	6.1	>5
223	3.1	3.8
224	8.6	>5

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
225	>200	--
226	13	--
227	1.4	>5
228	1.4	1.3
229	4.2	2.2
230	1.2	4.3
231	>200	>5
232	2.0	>5
233	7.5	--
234	0.8	0.65
235	>200	>5
236	14	>5
237	3.6	2.0
238	20	--
239	24	--
240	20	--
241	1.8	--

ID No.	TR-FRET K_i (μM)	RANT IC_{25} (μM)
242	0.50	1.5
243	0.60	1.2
244	0.40	2.4
245	0.80	1.7
246	1.6	>5
247	>200	>5
248	>200	>5
249	22	>5
250	11	>5
251	19	--
252	>200	>5
253	14	>5
254	1.8	>5
255	8.8	1.25
256	42	>5
257	5.7	2.7

Table G

ID No	BLI K_d (μM)	RANT IC_{50} (μM)
262	5.2	6.6
263	0.61	>100
264	0.18	>100
265	0.72	>100
266	0.69	7.8

ID No	BLI K_d (μM)	RANT IC_{50} (μM)
267	8.0	>21
268	8.7	2.9
269	1.4	>100
270	0.51	0.36
271	0.13	>100

ID No	BLI K_d (μM)	RANT IC_{50} (μM)
272	7.7	2.0
273	0.14	0.39
274	0.20	11
275	0.062	20
276	0.041	12
277	0.020	1.5
278	0.083	21
279	0.25	2.4
280	0.88	35
281	0.46	17
282	0.14	0.67
283	0.090	2.4
284	0.35	1.8
285	0.12	0.90
286	2.6	10
287	1.5	1.4
288	9.6	2.0
289	5.0	2.4
290	>20	8.3
291	3.8	1.8
292	5.5	13
293	3.5	ND
294	0.30	13
295	0.35	41
296	5.3	3.0

ID No	BLI K_d (μM)	RANT IC_{50} (μM)
297	2.7	2.9
298	6.6	1.4
299	0.24	3.8
300	0.35	8.6
301	ND	13
302	8.2	9.1
303	0.18	>100
304	1.4	5.9
305	23	18
306	1.2	14
307	ND	>82
308	0.56	>100
309	1.4	41
310	0.97	38
311	2.3	20
312	1.3	7.4
313	4.7	>100
314	3.0	>60
315	11	>100
316	3.4	10
317	5.0	5.0
318	6.0	16
319	7.8	12
320	100	1.9
321	0.71	3.5

[00880] **References**

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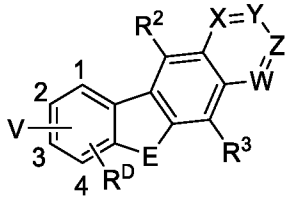
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WE CLAIM:

1. A compound, or pharmaceutically acceptable salt thereof, having a structure of Formula (I):



(I)

wherein

one or two of W, X, Y, and Z is N and the others are CR^4, or each of W, X, Y, and Z is CR^4;

E is NR^6, O, or S;

V is H, halo, OR^1, $C(O)NR^NR^1$, $C(O)OR^1$, or NR^AR^B;

R^1 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}cyanoalkyl, C_{1-6}hydroxyalkyl, C_{1-6}alkylene-C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-$C(O)C_{1-6}$alkyl, C_{0-6}alkylene-CO_2R^N, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-aryl, C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-$C(O)NR^AR^B$, $C(O)$-C_{3-14}carbocyclyl, or $C(O)$-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, aryl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

each of R^2, R^3, and R^4 is independently H, halo, CN, OH, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylene-aryl, NR^AR^B, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), $C(O)C_{3-14}$carbocyclyl, CO_2H, $C(O)NR^N$-C_{1-6}alkylene-NR^AR^B, or C_{1-6}alkylene-NR^AR^B, and the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with 1 or 2 R^C groups;

R^6 is H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and carbocyclyl, heterocyclyl, aryl or heteroaryl is optionally substituted with 1 or 2 R^C;

R^A and R^B are independently H, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkylene-C_{1-6}alkoxy, $SO_{0-2}C_{1-6}$alkyl, SO_{0-2}aryl, $C(O)C_{1-6}$alkyl, C_{1-6}alkylene-$N(R^N)R^N$, C_{1-6}alkylene-$C(O)NR^NR^N$, $C(O)C_{3-14}$carbocyclyl, C_{0-6}alkylene-C_{3-14}carbocyclyl, C_{0-}

$_6$alkylene-aryl, C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{0-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S), and the carbocyclyl, heterocyclyl, or heteroaryl is optionally substituted with 1 or 2 R^C groups; or

R^A and R^B together with the nitrogen to which they are attached can form a 4-8 membered heterocyclyl comprising 0-2 additional ring heteroatoms selected from N, O, and S, and the heterocyclyl is optionally substituted with 1 or 2 R^C groups and optionally has a spiro cyclopropyl substituent;

each R^N is independently H or C_{1-4}alkyl;

each R^C is independently halo, OH, oxo, NR^NR^N, C_{1-6}alkyl, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, CO_2C_{1-6}alkyl, or C_{0-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S); and

R^D is H, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

with the proviso that when R^2 and R^3 are each Me, R^D is H, V is OR^1, Y is N, and each of W, X, and Z is CR^4, then

(i) X is CH and OR^1 is not OH or OMe; or

(ii) E is not NH or NMe; or

(iii) OR^1 is not at the 2-position.

2. The compound or salt of claim 1, wherein V is at the 1-position.

3. The compound or salt of claim 1, wherein V is at the 2-position.

4. The compound or salt of claim 1, wherein V is at the 3-position.

5. The compound or salt of claim 1, wherein V is at the 4-position.

6. The compound or salt of any one of claims 2 to 5, wherein V is OR^1.

7. The compound or salt of any one of claims 2 to 5, wherein V is $C(O)NR^NR^1$ or $C(O)R^1$.

8. The compound or salt of claim 6 or 7, wherein R^1 is C_{1-6}alkyl, C_{0-6}alkylene-CO_2R^N, C_{1-6}alkylene-$C(NH)NR^AR^B$, C_{1-6}alkyleneNR^{A}R^B, C_{1-6}alkylene-$C(O)NR^AR^B$, or C_{1-6}alkylene(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S).

9. The compound or salt of claim 8, wherein R^1 is C_{1-6}alkyleneNR^{A}R^B.

10. The compound or salt of claim 9, wherein R^1 is C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-(N-methylpiperazinyl), C_{1-6}alkylene-morpholinyl, C_{1-6}alkylene-$N(Me)_2$, C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-$N(Et)_2$, C_{1-6}alkylene-pyrrolidinyl, C_{1-6}alkylene-dihydroimidazolyl, or C_{1-6}alkylene-piperidinyl.

11. The compound or salt of claim 8, wherein R^1 is C_{1-6}alkylene-C(NH)NR^AR^B.

12. The compound or salt of claim 11, wherein R^1 is C_{1-6}alkylene-C(NH)NH_2.

13. The compound or salt of claim 8, wherein R^1 is C_{1-6}alkylene(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S).

14. The compound or salt of claim 13, wherein R^1 is C_{1-6}alkylene-(4,5-dihydro-2-imidazolyl).

15. The compound or salt of claim 8, wherein R^1 is C_{1-6}alkylene-C(O)NR^AR^B.

16. The compound or salt of claim 15, wherein R^1 is C_{1-6}alkylene-C(O)NH_2, C_{1-6}alkylene-C(O)NMe_2, C_{1-6}alkylene-C(O)NHMe, C_{1-6}alkylene-C(O)-piperazinyl, C_{1-6}alkylene-C(O)-(methylpiperazinyl), C_{1-6}alkylene-C(O)NHC_{1-6}alkylene-morpholinyl, C_{1-6}alkylene-C(O)NHC_{1-6}alkylene-NH_2, C_{1-6}alkylene-C(O)NHC_{1-6}alkylene-NHMe, or C_{1-6}alkylene-C(O)NHC_{1-6}alkylene-NMe_2.

17. The compound or salt of any one of claims 2 to 5, wherein V is NR^AR^B.

18. The compound or salt of claim 17, wherein V is piperazinyl optionally substituted with methyl or optionally comprising a spiro cyclopropyl substituent.

19. The compound or salt of any one of claims 1 to 18, wherein E is O.

20. The compound or salt of any one of claims 1 to 18, wherein E is S.

21. The compound or salt of any one of claims 1 to 18, wherein E is NR^6.

22. The compound or salt of claim 21, wherein R^6 is C_{1-6}alkyl or C_{1-6}haloalkyl.

23. The compound or salt of claim 21, wherein R^6 is H or Me.

24. The compound or salt of claim 21, wherein R^6 is C_{1-6}alkylene-NR^AR^B.

25. The compound or salt of claim 24, wherein R^6 is C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-(methylpiperazinyl), C_{1-6}alkylene-morpholinyl, C_{1-6}alkylene-$N(Me)_2$, C_{1-6}alkylene-piperazinyl, C_{1-6}alkylene-$N(Et)_2$, C_{1-6}alkylene-pyrrolidinyl, or C_{1-6}alkylene-piperidinyl.

26. The compound or salt of claim 21, wherein R^6 is C_{1-6}alkylene- C_{3-14}carbocyclyl, C_{1-6}alkylene-(3-14 membered heterocyclyl having 1-3 ring heteroatoms selected from N, O and S), C_{1-6}alkylene-aryl, C_{1-6}hydroxyalkylene-aryl, or C_{1-6}alkylene-(5-10 membered heteroaryl having 1-3 ring heteroatoms selected from N, O and S).

27. The compound or salt of claim 26, wherein R^6 is benzyl, C_{1-6}hydroxyalkylenephenyl, C_{1-6}alkylene-pyridinyl, C_{1-6}alkylene-tetrahydrothiophenedioxide, C_{1-6}alkylene-imidazoyl, C_{1-6}alkylene-(methylimidazolyl), or C_{1-6}alkylene-(4,5-dihydro-2-imidazolyl).

28. The compound or salt of any one of claims 1 to 27, wherein R^2 is H.

29. The compound or salt of claim 28, wherein R^3 is Me.

30. The compound or salt of any one of claims 1 to 27, wherein R^2 is Me.

31. The compound or salt of claim 30, wherein R^3 is Me.

32. The compound or salt of any one of claims 1 to 27, wherein R^2 is OH.

33. The compound or salt of any one of claims 1 to 28, 30, and 32, wherein R^3 is H.

34. The compound or salt of any one of claims 1 to 28, 30, and 32, wherein R^3 is Me.

35. The compound or salt of any one of claims 1 to 28, 30, and 32, wherein R^3 is F or CF_3.

36. The compound or salt of any one of claims 1 to 35, wherein X is N and W, Y, and Z are each CR^4.

37. The compound or salt of claim 36, wherein each R^4 is H.

38. The compound or salt of any one of claims 1 to 35, wherein Y is N and W, X, and Z are each CR^4.

39. The compound or salt of claim 38, wherein each R^4 is H.

40. The compound or salt of any one of claims 1 to 35, wherein Z is N and W, X, and Y are each CR^4.

41. The compound or salt of claim 40, wherein each R^4 is H.

42. The compound or salt of any one of claims 1 to 35, wherein W is N and X, Y, and Z are each CR^4.

43. The compound or salt of claim 42, wherein each R^4 is H.

44. The compound or salt of any one of claims 1 to 35, wherein each of X, Y, Z, and W is CR^4.

45. The compound or salt of claim 44, wherein each R^4 is H.

46. The compound or salt of any one of claims 1 to 54, wherein each R^4 is independently H, CO_2H, $C(O)NR^N$-C_1-C_6-alkylene-NR^AR^B, or $C_{1\text{-}6}$alkylene-NR^AR^B.

47. The compound or salt of claim 46, wherein one R^4 is CO_2H, $C(O)NR^N$-C_1-C_6-alkylene-NR^AR^B, or $C_{1\text{-}6}$alkylene-NR^AR^B, and all other R^4 are H.

48. The compound or salt of claim 46 or 47, wherein at least one R^4 is $C(O)NHC_{1-6}alkyleneNMe_2$ or CO_2H.

49. The compound or salt of any one of claims 1 to 48, wherein R^D is H.

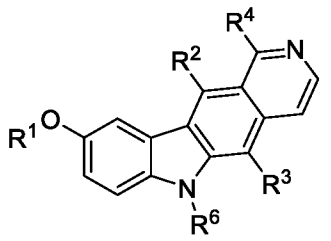
50. The compound or salt of any one of claims 1 to 48, wherein R^D is F or Cl.

51. A compound, or pharmaceutically acceptable salt thereof, as listed in Table A.

52. A compound, or pharmaceutically acceptable salt thereof, as listed in Table B.

53. A compound, or pharmaceutically acceptable salt thereof, as listed in Table C.

54. A compound, or pharmaceutically acceptable salt thereof, having a structure of Formula (Xa):



(Xa)

wherein

R^1 is H, C_{1-6}alkyl, C_{1-6}alkylene-$C(O)C_{1-6}$alkyl, C_{1-6}alkylene-NR^AR^B, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), or C(O)-(3- to 14-membered heterocyclyl), wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S; and the heterocyclyl is optionally substituted with 1 or 2 R^C groups;

R^A and R^B are independently selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $S(O)_{0-2}$-C_{1-6}alkyl, $S(O)_{0-2}$-aryl, $C(O)C_{1-6}$alkyl, $C(O)C_{3-14}$carbocyclyl, C_{3-14}carbocyclyl, C_{1-6}alkylene-C_{3-14}carbocyclyl, aryl, 3- to 14-membered heterocyclyl, C_{1-6}alkylene-(3- to 14-membered heterocyclyl), and 5- to 10-membered heteroaryl, and wherein 1-4 heteroaryl or 1-4 heterocyclyl ring atoms are independently selected from N, O, and S, and the carbocyclyl, aryl, heteroaryl, or heterocyclyl is optionally substituted with 1 or 2 R^C groups;

each R^C is independently halo, OH, C_{1-6}alkoxy, $C(O)C_{1-6}$alkyl, $C(O)OC_{1-6}$alkyl, C_{1-6}alkyl, 3- to 14-membered heterocyclyl, and wherein 1-4 heterocyclyl ring members are independently selected from N, O, and S;

R^4 is H, C_{1-6}alkyl, NR^AR^B, $C(O)OC_{1-6}$alkyl, $C(O)NR^A$-C_{1-6}alkylene-NR^AR^B, or $C(O)NR^A$–C_{1-6}alkylene-OR^B;

R^2 and R^3 are each independently H or CH_3; and

R^6 is H or CH_3.

55. A pharmaceutical composition comprising the compound or salt of any one of claims 1 to 54 and a pharmaceutically acceptable excipient.

56. A method of treating a subject suffering from a disease or condition characterized by an expanded G_4C_2 repeat RNA ($r(G_4C_2)^{exp}$) comprising administering a therapeutically effective amount of the compound or salt of any one of claims 1 to 54.

57. The method of claim 56, wherein the disease or condition is amyotrophic lateral sclerosis (ALS) or frontotemporal dementia (FTD).

58. The method of claim 56, wherein the method comprises inhibiting a RAN translation which produces toxic dipeptide repeat proteins.

59. The method of claim 58, where the method comprises inhibiting nuclear foci.

60. The method of claim 58 or 59, wherein the method comprises rescue of nuclear pore dysfunction.

61. The method of any one of claims 58 to 60, wherein the method comprises rescue of protein localization.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/49357

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/502; A61K 31/52; A61K 31/551 (2021.01)

CPC - A61K 31/337; A61K 31/475; A61K 31/502; A61K 31/5025

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.
X	US 2004/0186132 A1 (JONES et al.) 23 September 2004 (23.09.2004), especially: para [0019] formula.	1-5
A	STIBOROVA et al. "Ellipticine cytotoxicity to cancer cell lines - a comparative study", Interdiscip. Toxicol. 2011. Vol. 4(2): pp 98-105, especially: pg 99, Figure 1, ellipticine.	1-5
A	US 2007/0021391 A1 (DOI et al.) 25 January 2007 (25.01.2007), especially: para [0119] 1H-pyrido[2,3-b]carbazole.	1-5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2021 (11.11.2021)	FEB 04 2022
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Kari Rodriquez Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 21/49357

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.: 8-16, 19-50 and 55-61
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
(see extra sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 21/49357

--BOX III - LACK OF UNITY--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I+: Claims 1-7, 17-18 and 51-54 directed to a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The compound of Formula (I) will be searched to the extent that it encompasses the first species of claim 1, wherein W is N, and X, Y, and Z are CR4; E is NR6; V is H; R2, R3 and R4 are H; R6 is H; RD is H; with the proviso that when R2 and R3 are each Me, RD is H, V is OR1, Y is N, and each of W, X, and Z is CR4, then (i) X is CH and OR1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR' is not at the 2-position. It is believed that claims 1-5 encompass this first named invention, and thus these claims will be searched without fee to the extent that they encompass the first species of claim 1. Applicant is invited to elect additional compounds of Formula (I), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of claim 1, wherein W is CR4, X is N, Y and Z are CR4; E is NR6; V is H; R2, R3 and R4 are H; R6 is H; RD is H; with the proviso that when R2 and R3 are each Me, RD is H, V is OR1, Y is N, and each of W, X, and Z is CR4, then (i) X is CH and OR1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR' is not at the 2-position (i.e. claims 1-5).

The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Group I+.

Common technical features:

The inventions of Groups I+ share the technical feature of a compound having the structure of Formula (I).

These shared technical features, however, do not provide a contribution over the prior art, as being anticipated by the article entitled "Ellipticine cytotoxicity to cancer cell lines - a comparative study" by Stiborova et al. (hereinafter 'STIBOROVA').

Stiborova teaches a compound having a structure of Formula (I) wherein W, X and Z are CR4, Y is N; E is NR6; V is H; R2 and R3 are C1 alkyl; R6 is H; RD is H; with the proviso that when R2 and R3 are each Me, RD is H, V is OR1, Y is N, and each of W, X, and Z is CR4, then (i) X is CH and OR1 is not OH or OMe; or (ii) E is not NH or NMe; or (iii) OR' is not at the 2-position (pg 99, Figure 1, ellipticine).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I+.

The inventions of Group I+ thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 8-16, 19-50 and 55-61 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).