

NOVEL SYNTHESIS OF SUBSTITUTED TRICYCLIC COMPOUNDS

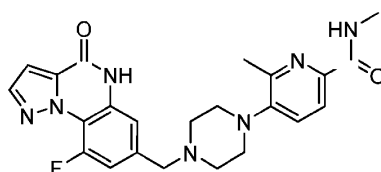
FIELD OF THE INVENTION

[0001] Described herein is a process for preparing substituted tricyclic compounds that can be used as inhibitors of poly-ADP ribose polymerase (PARP), in particular, inhibitors that exhibit
 5 selectivity for inhibiting PARP1 relative to PARP2.

BACKGROUND OF THE INVENTION

[0002] Research indicates that the human genome may encode 17 different poly-ADP ribose polymerases (PARPs). See Vyas et al., Nature Communications 4:2240 at 2 and Table 1 (DOI: 10.1038/ncomms3240). Inhibitors of PARPs may be useful in the treatment of various cancers.
 10 See WO2023025307A1.

[0003] The compound 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one, having the chemical structure of formula (III) shown below (alternatively named 5-(4-((9-fluoro-4-oxo-4,5-dihydropyrazolo[1,5-a]quinoxalin-7-yl)methyl)piperazin-1-yl)-N,6-dimethylpicolinamide), and having the chemical formula $C_{23}H_{24}FN_7O_2$, is disclosed and described in WO 2023/025307.
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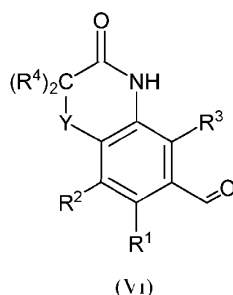
(III)

7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one

20 [0004] The present disclosure provides alternative processes for synthesizing the compound of formula (III) and related compounds.

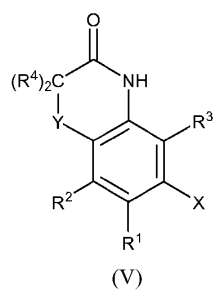
SUMMARY OF THE INVENTION

[0005] In an aspect, the present disclosure provides a process for preparing a compound of formula (VI):



comprising the steps of:

- (i) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



- (ii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vi) maintaining the mixture for 5 minutes to overnight e.g. about 20 minutes at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours e.g. 10 minutes;
- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) warming the mixture of step (viii) to room temperature over about 2 hours,

(x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and

(xi) optionally purifying the product,

wherein:

5 X is Br or I,

Y is C, NH, NR⁵, O or S,

each of R¹ through R⁵ is independently H, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl,

10 or independently any two of R¹ through R⁵ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl,

or independently any two of R¹ through R⁵ may form a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

15 and each of R¹ through R⁵ independently may be substituted with R¹⁵,

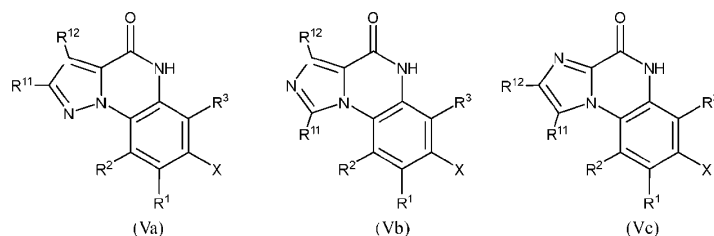
and

each R₁₅ is independently selected from cyano, amino, nitro, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocycloalkyl, aryl, and heteroaryl, and

20 wherein each of R¹ through R⁵ and R¹⁵, including any ring or rings they may form, independently optionally comprises at least one group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

[0006] In some embodiments of the process for preparing a compound of formula (VIII) provided herein, Y is C. In some embodiments, Y is NH. In some embodiments, Y is NR⁵. In some
25 embodiments, Y is O. In some embodiments, Y is S.

[0007] In some embodiments, Y, R⁴ and R⁵ are defined such that the compound of formula (V) has the structure (Va), (Vb) or (Vc):



wherein R^{11} and R^{12} are each independently H, F, methyl, C_2 - C_8 alkyl that is saturated or unsaturated, C_3 - C_8 cycloalkyl or heterocycloalkyl that is saturated or unsaturated, C_3 - C_8 aryl or heteroaryl, $-CO_2H$, $-CONHR^{15}$, or $-CONH_2$,
and each of R^{11} and R^{12} independently is optionally substituted with R^{15} .

5 [0008] In some embodiments, the compound of formula (V) has the structure (Va). In some embodiments, the compound of formula (V) has the structure (Vb). In some embodiments, the compound of formula (V) has the structure (Vc).

[0009] In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is Br or X is I, and all R groups present are H. In some embodiments, X is Br or X is I, R^2 is F,
10 and R^1 and R^3 through R^5 and R^{15} are H. In some embodiments, X is Br or X is I, and none of R^1 through R^5 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

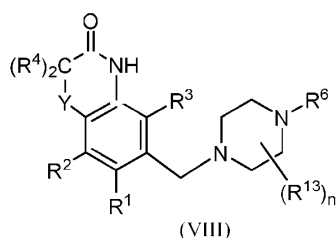
[0010] In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, R^2 is F, and R^1 , R^3 and R^{15} are H. In some embodiments in which the compound
15 of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, and none of R^1 , R^3 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

[0011] In some embodiments, the process includes the step of adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at $-25^\circ C$ following step (vi). In some
20 embodiments, the reaction temperature is maintained at $-25^\circ C$, for 5 minutes to 3 hours e.g. for 10 minutes, 30 minutes or one hour. In some embodiments, the process does not include the step of adding 0.25 to 1 equivalent additional *n*-BuLi.

[0012] In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

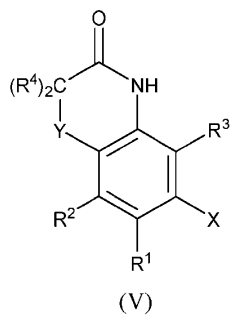
[0013] In some embodiments, the process includes the step of purifying the product at step
25 (xi). In some embodiments, the process does not include the step of purifying the product at step (xi).

[0014] In another aspect, the present disclosure provides a process for preparing a compound of formula (VIII):

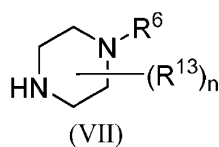


wherein the process comprises the steps of:

- (i) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



- (ii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- 5 (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to
- 10 obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- 15 (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to
- 20 warm to -5°C to 0°C;
- (ix) warming the mixture of step (viii) to room temperature over about 2 hours,
- (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xi) optionally purifying the product,
- 25 (xii) combining the product of step (xi) with 1 equivalent of a compound of formula (VII):



- , or a salt thereof, e.g. an acid salt such as the hydrochloride salt, in about 50 volumes, relative to the compound of formula (V) on a volume-to-mass basis, of a solvent selected from 2-methyl-tetrahydrofuran (2-MeTHF), dichloromethane (DCM), dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), isopropyl acetate (IPAc), dimethylacetamide (DMAc), isopropyl alcohol (IPA), ethanol (EtOH), tetrahydrofuran (THF), dimethylformamide (DMF), ethyl acetate (EtOAc), and acetonitrile (MeCN), for example, THF, and about 4 equivalents of acetic acid;
- (xiii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;
- (xiv) adding 2 to 3 equivalents of sodium triacetoxyborohydride ((CH₃COO)₃BHNa) and stirring overnight at about 20°C to about 25°C; and
- (xv) optionally purifying the product,

wherein:

X is Br or I,

Y is C, NH, NR⁵, O or S,

each of R¹ through R⁶ and R¹³ is independently H, F, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl, -CO₂H, -CONHR¹⁵, -CONH₂, or independently any two of R¹ through R⁵ and any two R¹³ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl,

or independently any two of R¹ through R⁵ and any two R¹³ may form a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

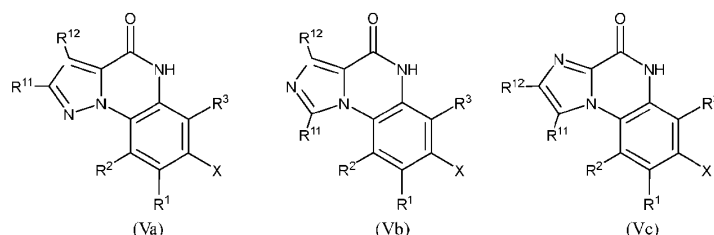
and each of R¹ through R⁶ and R¹³ independently is optionally substituted with R¹⁵, n is from 0 to 8, and

each R₁₅ is independently selected from cyano, amino, nitro, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocyclyl, aryl, and heteroaryl, and

wherein each of R¹ through R⁶ and R¹³ and R¹⁵, including any ring or rings they may form, independently optionally comprises at least one group selected from –

C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

- [0015] In some embodiments of the process for preparing a compound of formula (VIII) provided herein, Y is C. In some embodiments, Y is NH. In some embodiments, Y is NR⁵. In some
 5 embodiments, Y is O. In some embodiments, Y is S. In some embodiments, Y, R⁴ and R⁵ are defined such that the compound of formula (V) has the structure (Va), (Vb) or (Vc):



- wherein R¹¹ and R¹² are each independently H, F, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, C₃-C₈ aryl or
 10 heteroaryl, -CO₂H, -CONHR¹⁵, or -CONH₂,
 and each of R¹¹ and R¹² independently is optionally substituted with R¹⁵.

- [0016] In some embodiments, the compound of formula (V) has the structure (Va). In some embodiments, the compound of formula (V) has the structure (Vb). In some embodiments, the compound of formula (V) has the structure (Vc).

- [0017] In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is Br or X is I, and all R groups present are H. In some embodiments, X is Br or X is I, R² is F, and R¹ and R³ through R⁵ and R¹⁵ are H. In some embodiments, X is Br or X is I, and none of R¹ through R⁵ and R¹⁵ comprise a group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

- [0018] In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, R² is F, and R¹, R³ and R¹⁵ are H. In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, and none of R¹, R³ and R¹⁵ comprise a group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

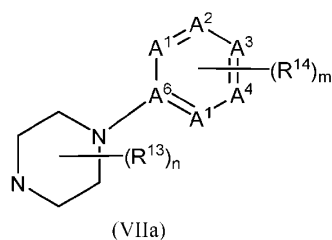
- [0019] In some embodiments, the process includes the step of adding 0.25 to 1 equivalent additional n-BuLi and maintaining the reaction temperature at -25°C following step (vi). In some embodiments, the reaction temperature is maintained at -25°C, for 5 minutes to 3 hours e.g. for 10 minutes, 30 minutes or one hour. In some embodiments, the process does not include the step of adding 0.25 to 1 equivalent additional n-BuLi.

[0020] In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

[0021] In some embodiments, the process includes the step of purifying the product at step (xi). In some embodiments, the process does not include the step of purifying the product at step (xi).

- 5 [0022] In some embodiments, the free base (VII) is used in step (xii). In some embodiments, a salt of the free base (VII) is used, e.g. the hydrochloride salt of (VII).

[0023] In some embodiments of the process for preparing a compound of formula (VIII) provided herein, the compound of structure (VIIa) is used:



, or a salt thereof,

- 10 [0024] wherein:

[0025] each of A¹, A², A³, A⁴, A⁵ and A⁶ is independently selected from N and C,

[0026] m=0 to 5,

[0027] wherein each R¹⁴ is independently H, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl,

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[0028] or independently any two R¹⁴ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl, or independently any two R¹⁴ may form a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

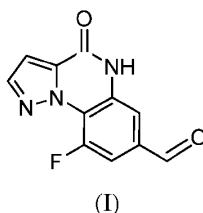
- 20 [0029] each R¹⁴ independently may be substituted with R¹⁵,

[0030] each R¹⁴ (including any ring or rings they may form) independently optionally comprises at least one group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-,

[0031] and R¹³, n and R¹⁵ are as defined herein.

- 25 [0032] In some embodiments, m and n are both 0. In some embodiments, n is 0 and m is selected from 1, 2, 3, 4 and 5. In some embodiments, n is 0 and m is 1. In some embodiments, n is 0, m is 1 and R¹⁴ is unsubstituted and is methyl or C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl.

- [0033] In some embodiments, 0, 1, 2, 3, or 4 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remainder are C. In some embodiments, any 1 of A¹, A², A³, A⁴, A⁵ and A⁶ is N and the remaining 5 are C. In some embodiments, any 2 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 4 are C. In some embodiments, any 3 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 3 are C. In some embodiments, any 4 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 2 are C.
- [0034] In some embodiments, the free base form of (VIIa) is used. In some embodiments, a salt form of (VIIa) is used, e.g. the hydrochloride salt. In some embodiments, the compound of formula (VII) or (VIIa) has the structure of the compound of formula (IV) disclosed herein, or of formula (IVa) or a salt thereof, disclosed herein.
- [0035] In some embodiments, the product of step (x) is purified. In some embodiments, in step (v), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (vi), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (viii), 4 equivalents of dry DMF is added.
- [0036] In a further aspect, the present disclosure provides a process for preparing a compound of formula of (I):



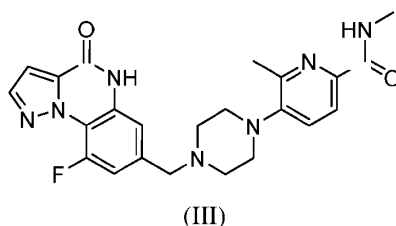
comprising the steps of:

- (i) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)
- (II) ;
- (ii) cooling the mixture of (II) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;

- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C ;
- 5 (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- 10 (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) permitting the temperature to warm to room temperature over about 2 hours,
- 15 (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xi) optionally purifying the product.

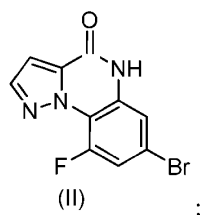
[0037] In some embodiments, the product of step (x) is purified. In some embodiments, in step (v), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (vi), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

[0038] In a further aspect, the present disclosure provides a process for preparing 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-
25 a]quinoxalin-4(5H)-one having a formula of (III):

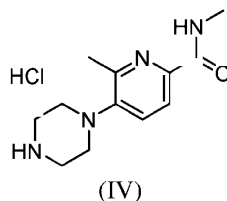


comprising the steps of:

- (i) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)



- (ii) cooling the mixture of (II) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- 5 (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- 10 (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- 15 (viii) adding between about 2 and 10 equivalents of dry dimethylformamide ((CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) permitting the temperature to warm to room temperature over about 2 hours,
- 20 (x) adding about 1/50 volume of water to quench the reaction;
- (xi) optionally purifying the product;
- (xii) combining the product of step (xi) with 1 equivalent of N,6-dimethyl-5-(piperazin-1-yl)picolinamide hydrochloride having a formula of (IV):

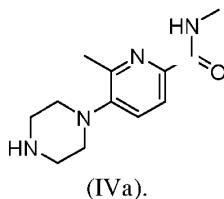


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in about 50 volumes of a solvent selected from THF, DMF, EtOAc, and MeCN, for example, THF, and about 4 equivalents of acetic acid;

- (xiii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;
- (xiv) adding 2 to 3 equivalents of sodium triacetoxyborohydride and stirring overnight at about 20°C to about 25°C; and
- (xv) optionally purifying the product.

5 [0039] In some embodiments, the free base form of (IV) is used, referred to herein as (IVa):



[0040] In some embodiments, a salt of (IVa) is used other than the hydrochloride salt, e.g. the HBr salt.

10 [0041] In some embodiments, the product of step (x) is purified. In some embodiments, in step (v), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (vi), the internal reaction temperature is maintained at -20°C or from below -20° C to -40°C or from -20°C to -30°C. In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

15 **BRIEF DESCRIPTION OF THE DRAWINGS**

[0042] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

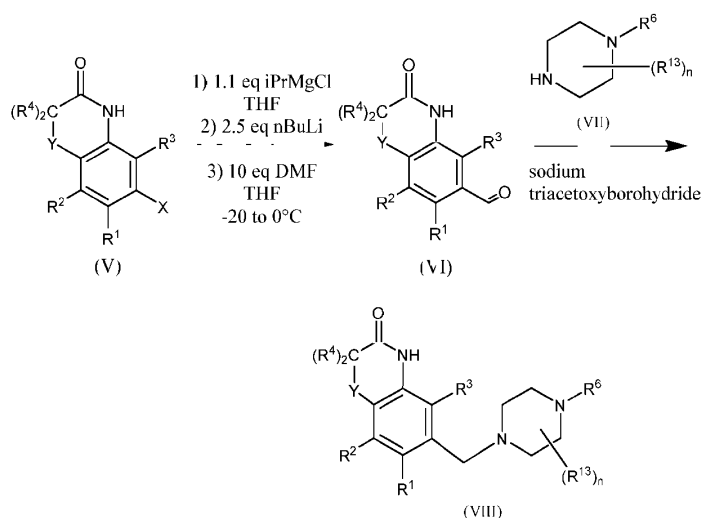
[0043] FIG. 1 presents a ¹H NMR spectrum of the compound of structure (I).

20 [0044] FIG. 2 presents a ¹H NMR spectrum of the compound of structure (III).

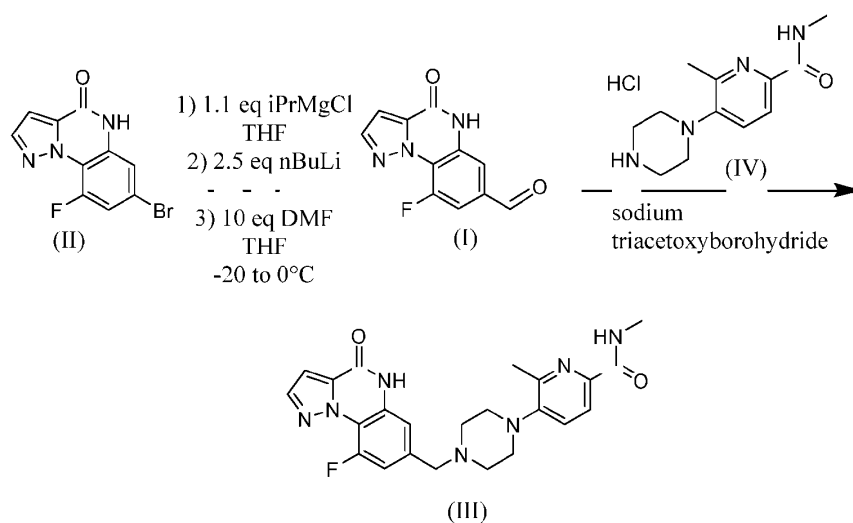
[0045] FIGs. 3A-3I present LCMS data from Example 2, preparation of (I) from (II) and preparation of (III) from (I).

DETAILED DESCRIPTION

25 [0046] The present disclosure provides a process for preparing compounds of the general formula (VIII) from a compound of general formula (V) via the aldehyde intermediate (VI), which is combined with the compound of general formula (VII) as summarized below:



[0047] The present disclosure further provides a process for preparing the compound of formula (III) from a compound of formula (II) via the aldehyde intermediate (I), which is combined with the compound of formula (IV) as summarized below:



5

[0048] WO2023025307 provides a current process for synthesizing 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one (see scheme 7 on page 46).

[0049] The process of WO '307, diagrammed below, uses a Pd catalyst which is expensive and the catalyst loading used is high (5%). These features are significant cost drivers for the

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API. The process of WO '307 also uses Bu_3SnOH , which is toxic. Stoichiometric amounts of stannane waste are difficult and expensive to remove at scale.

[0050] The process of WO '307 also uses SOCl_2 , which is a highly corrosive chemical.

[0051] The WO '307 process's N-alkylation step employing a benzyl chloride is a messy reaction that leads to formation of side products such as the doubly alkylated product. In addition, the benzyl chloride substrate employed by the WO '307 process is a potentially mutagenic impurity with a positive Ames test result. It needs to be purged in the API process and the content needs to be limited to trace levels (<50ppm).

[0052] The process disclosed herein for synthesizing 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one has the following improvements and presented certain challenges to develop.

[0053] In order to remove one synthetic step, carbon must be added at the correct oxidation stage.

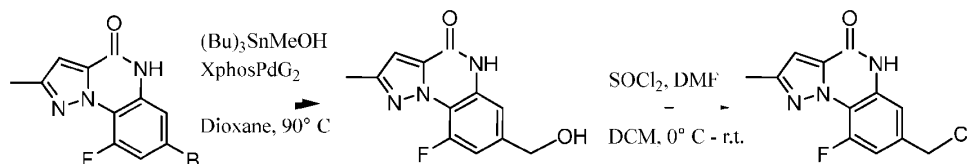
[0054] The process disclosed herein involves aldehyde formation through metal halogen exchange of a heteroaryl bromide with a Grignard and/or butyl lithium, followed by quenching of the metalated species with a formylating agent such as DMF. However, the hetero aryl substrate contains an acidic proton, which will quench the Grignard and/or butyl lithium. It is not intuitive how this can be overcome.

[0055] A combination of both a Grignard and n-butyl lithium is needed for this step to succeed. This combination is uncommon. Surprisingly, more than one equivalent of nBuLi was required for transformation, suggesting the formation of an 'ate' complex prior to the quench by DMF.

[0056] Unexpectedly, adjustment of both DMF and butyl lithium amounts were necessary for achieving high conversion in the new process. It was also unexpected that, in the process disclosed herein, the presence of the exact amount of HOAc and reducing agents such as sodium triacetylborohydride (STAB) is necessary to reduce side products and improve the conversion to the product.

[0057] The process disclosed herein is significantly more efficient, requiring 2 chemical steps instead of 3, is more economical at least by virtue of not using the expensive palladium catalyst, and is more scalable at least by virtue of eliminating stannane waste and avoiding the use of corrosive thionyl chloride, than the process disclosed in WO2023025307.

[0058] The process disclosed herein bypasses the Pd-catalyzed Stille coupling and the SOCl_2 -mediated benzyl chloride (see below) steps, so the use of the expensive palladium catalyst and toxic Bu_3SnMeOH can be avoided.



5 (see WO2023025307, p. 45-46, paragraph [0110]).

[0059] Potentially mutagenic benzyl chloride intermediates are no longer formed. Trace analysis of such benzyl chloride intermediates in API is no longer needed.

[0060] Compared to N-alkylation used in the process of WO '307, reductive amination is a cleaner way to form the N-C bond, avoiding formation of the double alkylation byproducts.

10

Definitions

[0061] In order for the present invention to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the specification. The publications and other reference materials referenced herein to describe the background of the invention and to provide additional detail regarding its practice are hereby incorporated by reference.

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[0062] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, exemplary methods, devices, and materials are now described. All technical and patent publications cited herein are incorporated herein by reference in their entirety. Nothing herein is to be construed as an admission that the invention is not entitled to ante-date such disclosure by virtue of prior invention.

20

[0063] As used throughout the description, where compositions are described as having, including, or comprising specific components, or where processes are described as having, including, or comprising specific process steps, it is contemplated that compositions of the present teachings also consist essentially of, or consist of, the recited components, and that the processes of the present teachings also consist essentially of, or consist of, the recited processing steps.

25

[0064] As used throughout the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element

or component can be any one of the recited elements or components and can be selected from a group consisting of two or more of the recited elements or components.

[0065] The use of the singular herein includes the plural (and vice versa) unless specifically stated otherwise. In addition, where the use of the term “about” is before a quantitative value, the present
5 teachings also include the specific quantitative value itself, unless specifically stated otherwise.

[0066] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present teachings remain operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0067] As used in the description and the appended claims, the singular forms “a,” “an,” and “the”
10 include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a composition” includes mixtures of two or more such compositions.

[0068] Throughout the description and claims of this specification the word “comprise” and other forms of the word, such as “comprising” and “comprises,” means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

[0069] “Optional” or “optionally” means that the subsequently described event or circumstance may
15 or may not occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[0070] *Improve, increase, or reduce*: As used herein, the terms “improve,” “increase,” or “reduce,” or grammatical equivalents, indicate values that are relative to a baseline measurement, such as a
20 measurement in the same individual prior to initiation of the treatment described herein, or a measurement in a control subject (or multiple control subject) in the absence of the treatment described herein. A “control subject” is a subject afflicted with the same form of disease as the subject being treated, who is about the same age as the subject being treated.

[0071] *In Vitro*: As used herein, the term “in vitro” refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, etc., rather than within a multi-cellular organism.
25

[0072] *In Vivo*: As used herein, the term “in vivo” refers to events that occur within a multi-cellular organism, such as a human and a non-human animal. In the context of cell-based systems, the term may be used to refer to events that occur within a living cell (as opposed to, for example, in vitro systems).
30

[0073] *Patient*: As used herein, the term “patient” or “subject” refers to any organism to which a provided composition may be administered, *e.g.*, for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (*e.g.*, mammals such as mice, rats,

rabbits, non-human primates, and humans). In some embodiments, a patient is a human. A human includes pre- and post-natal forms.

[0074] *Dry solvent*: as used herein, dry solvents are solvents that contain water at a level at or below 300 ppm, such as less than or equal to 300 ppm water, less than or equal to 250 ppm water, less than
5 or equal to 200 ppm water, less than or equal to 150 ppm water, and less than or equal to 100 ppm water. In embodiments herein, dry solvents have water at a level of less than 200 ppm.

[0075] *Pharmaceutically acceptable*: The term “pharmaceutically acceptable,” as used herein, refers to substances that, within the scope of sound medical judgment, are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other
10 problem or complication, commensurate with a reasonable benefit/risk ratio. Accordingly, pharmaceutically acceptable relates to substances that are not biologically or otherwise undesirable, *i.e.*, the material can be administered to an individual along with the relevant active compound without causing clinically unacceptable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

[0076] *Pharmaceutically acceptable form*: Unless otherwise indicated herein, any description of a formula or compound also includes any pharmaceutically acceptable forms of the compound. As used herein, a “pharmaceutically acceptable form” of a disclosed formula or compound includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers, polymorphs, prodrugs, and isotopically labeled derivatives of disclosed formulas and compounds. In embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, pharmaceutically acceptable salts, isomers,
20 prodrugs and isotopically labeled derivatives of disclosed compounds. In embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, pharmaceutically acceptable salts, stereoisomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt of a disclosed formula or compound as described herein.
25

[0077] *Pharmaceutically acceptable salt*: Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid, or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate,
30 benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate,

digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\text{-alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, sulfonate, and aryl sulfonate. Further pharmaceutically acceptable salts include salts formed from the quaternization of an amine using an appropriate electrophile, *e.g.*, an alkyl halide, to form a quaternized alkylated amino salt.

[0078] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the chemical or biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0079] The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted unless otherwise indicated. In embodiments, a variable group is unsubstituted. In embodiments, a variable group is substituted (*e.g.*, comprising 1, 2, 3, 4, or 5 substituents (*e.g.*, as described herein) and as valency and stability permits). Still further embodiments are described herein.

[0080] *Aliphatic*: As used herein, the term aliphatic refers to hydrocarbons and includes both saturated and unsaturated hydrocarbons. An aliphatic may be linear, branched, or cyclic. For example, C_1 – C_{20} aliphatics can include C_1 – C_{20} alkyls (*e.g.*, linear or branched C_1 – C_{20} saturated alkyls), C_2 – C_{20} alkenyls (*e.g.*, linear or branched C_4 – C_{20} dienylyls, linear, or branched C_6 – C_{20} trienylyls, and the like), and C_2 – C_{20} alkynyls (*e.g.*, linear or branched C_2 – C_{20} alkynyls). C_1 – C_{20} aliphatics can include C_3 – C_{20} cyclic aliphatics (*e.g.*, C_3 – C_{20} cycloalkyls, C_4 – C_{20} cycloalkenylyls, or C_8 – C_{20} cycloalkynylyls). In certain embodiments, the aliphatic may comprise one or more cyclic aliphatic and/or one or more heteroatoms such as oxygen, nitrogen, or sulfur and may optionally be substituted with one or more substituents such as alkyl, halo, alkoxyl, hydroxy, amino, aryl, ether, ester or amide. An aliphatic group is unsubstituted or substituted with one or more substituent groups as described herein. For example, an

aliphatic may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of **R'** independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is unsubstituted C₁-C₃ alkyl. In some embodiments, the aliphatic is unsubstituted. In some embodiments, the aliphatic does not include any heteroatoms.

[0081] *Alkyl*: As used herein, the term “alkyl” means acyclic linear and branched hydrocarbon groups, *e.g.*, “C₁-C₂₀ alkyl” refers to alkyl groups having 1–20 carbons and “C₁-C₄ alkyl” refers to alkyl groups having 1–4 carbons. Alkyl groups include C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, C₁-C₄ alkyl, and C₁-C₃ alkyl). In embodiments, an alkyl group is C₁-C₄ alkyl. An alkyl group may be linear or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, *etc.* The term “lower alkyl” means an alkyl group straight chain or branched alkyl having 1 to 6 carbon atoms. Other alkyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. An alkyl group may be unsubstituted or substituted with one or more substituent groups as described herein. For example, an alkyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of **R'** independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, C₁-C₄ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is unsubstituted C₁-C₃ alkyl. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like. In some embodiments, the alkyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6 substituent groups as described herein). In some embodiments, an alkyl group is substituted with a-OH group and may also be referred to herein as a “hydroxyalkyl” group, where the prefix denotes the -OH group and “alkyl” is as described herein. In some embodiments, an alkyl group is substituted with a-OR' group. Non-limiting examples of substituted alkyl groups include hydroxymethyl, chloromethyl, trifluoromethyl, aminomethyl, 1-chloroethyl, 2-hydroxyethyl, 1,2-difluoroethyl, 3-carboxypropyl, and the like. In substituent groups with multiple alkyl groups such as (C₁-C₆ alkyl)₂ amino, the alkyl groups may be the same or different.

[0082] *Alkylene*: The term “alkylene,” as used herein, represents a saturated divalent straight or branched chain hydrocarbon group and is exemplified by methylene, ethylene, isopropylene and the like. Likewise, the term “alkenylene” as used herein represents an unsaturated divalent straight or branched chain hydrocarbon group having one or more unsaturated carbon-carbon double bonds that may occur in any stable point along the chain, and the term “alkynylene” herein represents an

unsaturated divalent straight or branched chain hydrocarbon group having one or more unsaturated carbon-carbon triple bonds that may occur in any stable point along the chain. In certain embodiments, an alkylene, alkenylene, or alkynylene group may comprise one or more cyclic aliphatic and/or one or more heteroatoms such as oxygen, nitrogen, or sulfur and may optionally be substituted with one or more substituents such as alkyl, halo, alkoxy, hydroxy, amino, aryl, ether, ester or amide. For example, an alkylene, alkenylene, or alkynylene may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of **R'** independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is unsubstituted C₁-C₃ alkyl. In certain embodiments, an alkylene, alkenylene, or alkynylene is unsubstituted. In certain embodiments, an alkylene, alkenylene, or alkynylene does not include any heteroatoms.

[0083] *Alkenyl*: As used herein, "alkenyl" means any linear or branched hydrocarbon chains having one or more unsaturated carbon-carbon double bonds that may occur in any stable point along the chain, *e.g.*, "C₂-C₂₀ alkenyl" refers to an alkenyl group having 2-20 carbons. For example, an alkenyl group includes prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like. In some embodiments, the alkenyl comprises 1, 2, or 3 carbon-carbon double bond. In some embodiments, the alkenyl comprises a single carbon-carbon double bond. In some embodiments, multiple double bonds (*e.g.*, 2 or 3) are conjugated. An alkenyl group may be unsubstituted or substituted with one or more substituent groups as described herein. For example, an alkenyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of **R'** independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In some embodiments, **R'** independently is unsubstituted C₁-C₃ alkyl. In some embodiments, the alkenyl is unsubstituted. In some embodiments, the alkenyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6 substituent groups as described herein). In some embodiments, an alkenyl group is substituted with a-OH group and may also be referred to herein as a "hydroxyalkenyl" group, where the prefix denotes the -OH group and "alkenyl" is as described herein. Nonlimiting examples of alkenyl groups include ethenyl, 3-propenyl, 1-propenyl (*also* 2-methylethenyl), isopropenyl (*also* 2-methylethen-2-yl), buten-4-yl, and the like. Nonlimiting examples of substituted alkenyl groups include 2-chloroethenyl (*also* 2-chlorovinyl), 4-hydroxybuten-1-yl, 7-hydroxy-7-methyloct-4-en-2-yl, 7-hydroxy-7-methyloct-3,5-dien-2-yl, and the like.

[0084] *Alkynyl*: As used herein, “alkynyl” means any hydrocarbon chain of either linear or branched configuration, having one or more carbon-carbon triple bonds occurring in any stable point along the chain, *e.g.*, “C₂–C₂₀ alkynyl” refers to an alkynyl group having 2–20 carbons. Examples of an alkynyl group include prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, *etc.* In some embodiments, an alkynyl comprises one carbon-carbon triple bond. An alkynyl group may be unsubstituted or substituted with one or more substituent groups as described herein. For example, an alkynyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of **R'** independently is C₁–C₂₀ aliphatic (*e.g.*, C₁–C₂₀ alkyl, C₁–C₁₅ alkyl, C₁–C₁₀ alkyl, or C₁–C₃ alkyl). In some embodiments, **R'** independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁–C₂₀ alkyl, C₁–C₁₅ alkyl, C₁–C₁₀ alkyl, or C₁–C₃ alkyl). In some embodiments, **R'** independently is unsubstituted C₁–C₃ alkyl. In some embodiments, the alkynyl is unsubstituted. In some embodiments, the alkynyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6 substituent groups as described herein). Nonlimiting examples of alkynyl groups include ethynyl, prop-2-ynyl (*also* propargyl), propyn-1-yl, and 2-methyl-hex-4-yn-1-yl. Nonlimiting examples of substituted alkynyl groups include, 5-hydroxy-5-methylhex-3-ynyl, 6-hydroxy-6-methylhept-3-yn-2-yl, 5-hydroxy-5-ethylhept-3-ynyl, and the like.

[0085] *Alkoxy*: The term “alkoxy” refers to the group -O-alkyl, wherein the alkyl group is as defined above, including from 1 to 10 carbon atoms of a straight, branched, saturated cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy, cyclopropyloxy, cyclohexyloxy and the like. “Lower alkoxy” refers to alkoxy groups containing one to six carbons. In some embodiments, C₁₋₄ alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group can be optionally substituted by one or more substituents (*e.g.*, as described herein for alkyl). The terms “alkenoxy” and “alkynoxy” mirror the above description of “alkoxy” wherein the prefix “alk” is replaced with “alken” or “alkyn” respectively, and the parent “alkenyl” or “alkynyl” terms are as described herein.

[0086] *Amide*: The term “amide” or “amido” refers to a chemical moiety with formula C(O)N(R')₂, -C(O)N(R')-, -NR'C(O)R', or -NR'C(O)-, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring.

[0087] *Amino*: The term “amino” or “amine” refers to a $-N(R')_2$ group, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. In embodiments, an amino group is $-NHR'$, where R' is aryl (“arylamino”), heteroaryl (“heteroarylamino”), or alkyl (“alkylamino”).

[0088] *Aryl*: The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of six to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule, wherein at least one ring in the system is aromatic, and wherein each ring in the system contains 4 to 7 ring members. In some embodiments, an aryl group has 6 ring carbon atoms (“ C_6 aryl,” *e.g.*, phenyl). In some embodiments, an aryl group has 10 ring carbon atoms (“ C_{10} aryl,” *e.g.*, naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has 14 ring carbon atoms (“ C_{14} aryl,” *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Aryl groups can be unsubstituted or substituted. Exemplary aryls include phenyl, naphthyl, and anthracene. Aryl rings can be, for example, phenyl or naphthyl ring each optionally substituted with one or more moieties capable of replacing one or more hydrogen atoms. Non-limiting examples of aryl groups include: phenyl, naphthyl-1-yl, naphthyl-2-yl, 4-fluorophenyl, 2-hydroxyphenyl, 3-methylphenyl, 2-amino-4-fluorophenyl, 2-(*N,N*-diethylamino)phenyl, 2-cyanophenyl, 2,6-di-*tert*-butylphenyl, 3-methoxyphenyl, 8-hydroxynaphthyl-2-yl, 4,5-dimethoxynaphthyl-1-yl, and 6-cyano-naphthyl-1-yl. Aryl groups also include, for example, phenyl or naphthyl rings fused with one or more saturated or partially saturated carbon rings (*e.g.*, bicyclo[4.2.0]octa-1,3,5-trienyl, indanyl), which can be substituted at one or more carbon atoms of the aromatic and/or saturated or partially saturated rings.

[0089] *Arylalkyl*: The term “arylalkyl” refers to an $-(alkylene)-aryl$ radical where aryl and alkylene are as disclosed herein and which are optionally substituted by one or more of the exemplary substituent groups described herein. The “arylalkyl” group is bonded to the parent molecular structure through the alkylene moiety. The term “arylalkoxy” refers to an $-O-[arylalkyl]$ radical ($-O-[alkylene)-aryl]$), which is attached to the parent molecular structure through the oxygen. . Examples of arylalkyl groups include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl and the like.

[0090] *Arylene*: The term “arylene” as used herein refers to an aryl group that is divalent (that is, having two points of attachment to the molecule). Exemplary arylenes include phenylene (*e.g.*, unsubstituted phenylene or substituted phenylene).

5 [0091] *Carbonyl*: The term “carbonyl” refers to a $-C(=O)R'$, or $-C(=O)-$ group, where R' is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, amino, hydroxyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein.

10 [0092] *Cyclic*: The term “cyclic” as used herein, refers to any covalently closed structure. Cyclic moieties include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryls and heterocycloalkyls), aromatics (*e.g.*, aryls and heteroaryls), and non-aromatics (*e.g.*, cycloalkyls and heterocycloalkyls). In some embodiments, cyclic moieties are optionally substituted. In some embodiments, cyclic moieties form part of a ring system. Cyclic moieties can be unsaturated or saturated.

15 [0093] *Cycloaliphatic*: The term “cycloaliphatic” refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen and can be saturated or partially unsaturated. A cycloaliphatic group may be substituted or unsubstituted. Fully saturated cycloaliphatics can be termed “cycloalkyl”. Partially unsaturated cycloalkyl groups can be termed “cycloalkenyl” if the carbocycle contains at least one double bond, or “cycloalkynyl” if the carbocycle contains at least one triple bond. Cycloaliphatic groups include groups having from 3 to 13 ring atoms (*e.g.*, C_{3-13} cycloalkyl). Whenever it appears herein, a numerical range such as “3 to 10” refers to each integer in the given range; *e.g.*, “3 to 20 10 carbon atoms” means that the cycloaliphatic group (*e.g.*, cycloalkyl) can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term “cycloaliphatic” also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) 25 groups. Polycyclic cycloaliphatic groups include bicycles, tricycles, tetracycles, and the like. In some embodiments, “cycloalkyl” can be a C_{3-8} cycloalkyl group. In some embodiments, “cycloalkyl” can be a C_{3-5} cycloalkyl group. Illustrative examples of cycloaliphatic groups include but are not limited to the following moieties: C_{3-6} cycloaliphatic groups include, without limitation, cyclopropyl (C_3), cyclobutyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6) and the like. Examples of C_{3-7} cycloaliphatic groups include norbornyl (C_7). Examples of 30 C_{3-8} cycloaliphatic groups include the aforementioned C_{3-7} carbocyclyl groups as well as cycloheptyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C_{3-13} cycloaliphatic groups include the aforementioned C_{3-8} carbocyclyl groups as well as octahydro-1H indenyl, decahydronaphthalenyl, spiro[4.5]decanyl, 35 and the like. Additional, nonlimiting examples of cycloaliphatic groups (including cycloalkyl groups)

include: cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, 2,3-dihydroxycyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctanyl, decalanyl, 2,5-dimethylcyclopentyl, 3,5-dichlorocyclohexyl, 4-hydroxycyclohexyl, 3,3,5-trimethylcyclohex-1-yl, octahydropentalenyl, octahydro-1*H*-indenyl, 3a,4,5,6,7,7a-hexahydro-3*H*-inden-4-yl, decahydroazulenyl; bicyclo[6.2.0]decanyl, decahydronaphthalenyl, dodecahydro-1*H*-fluorenyl, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl. A “bicycloalkyl” group includes bridged cycloalkyl groups such as bicyclo[1.1.1]pentyl, bicyclo[2.1.1]heptane, adamantanyl, and norbornanyl; as well as spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane. A “heterobicycloalkyl” group is a bicycloalkyl comprising at least one heteroatom in the ring framework.

[0094] *Cyano*: The term “cyano” refers to a –CN group.

[0095] *Ester*: The term “ester” refers to a group of formula –C(O)OR’ or –R’OC(O)–, where R’ is selected from alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or heterocycloalkyl as described herein.

[0096] *Halogen* or *Halo*: As used herein, the term “halogen” or “halo” means fluorine, chlorine, bromine, or iodine.

[0097] *Haloalkyl*: The term “haloalkyl” is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Haloalkyl groups include perhaloalkyl groups, wherein all hydrogens of an alkyl group have been replaced with halogens (*e.g.*, –CF₃, CF₂CF₃). Haloalkyl groups can optionally be substituted with one or more substituents in addition to halogen. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, dichloroethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

[0098] *Haloalkoxy*: The term “haloalkoxy” refers to the group –O-haloalkyl, wherein the haloalkyl group is as defined above. Examples of haloalkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, and pentafluoroethoxy.

[0099] *Heteroalkyl*: The term “heteroalkyl” is meant a branched or unbranched alkyl, alkenyl, or alkynyl group as defined herein (including groups having from 1 to 14 carbon atoms) which also comprise at least one heteroatom (*e.g.*, 1, 2, 3 or 4 heteroatoms) independently selected from the group consisting of N, O, S, and P. Heteroalkyls include tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, hydrazones, imines, phosphodiesteres, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl group may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. Examples of heteroalkyls include polyethers, such as methoxymethyl and ethoxyethyl. Accordingly, the term

“heteroalkoxy” refers to the group -O-heteroalkyl, where the group is attached to the parent molecular structure via the oxygen.

[0100] Heteroalkylene: The term “heteroalkylenc,” as used herein, represents a divalent form of a heteroalkyl group as described herein.

- 5 **[0101] Heteroaryl:** The term “heteroaryl,” as used herein, is defined herein as one or more rings having from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), and wherein further at least one of the rings that includes a heteroatom is aromatic, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments, “heteroaryl” refers to a monocyclic, bicyclic, or tricyclic carbocyclic
- 10 ring system having a total of six to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 4 to 7 ring members, and wherein at least one ring atom is a heteroatom such as, but not limited to, nitrogen, oxygen, or sulfur. In heteroaryl groups that include 2 or more fused rings, the non-heteroatom bearing ring may be a carbocycle (*e.g.*, 6,7-Dihydro-5*H*-cyclopentapyrimidine) or aryl (*e.g.*, benzofuranyl, benzothiophenyl, indolyl). Exemplary heteroaryl groups have
- 15 from 5 to 14 ring atoms and contain from 1 to 5 ring heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heteroaryl group can be oxidized. Heteroaryl groups can be unsubstituted or substituted. The term “N-containing heteroaryl” refers to heteroaryl groups which comprise at least one nitrogen in the ring system (*e.g.*, a heteroaryl comprising 1, 2, or 3 nitrogen atoms). In some embodiments, the foregoing groups, as derived from the
- 20 groups listed above, are C-attached or N-attached where such is possible. Further, the term “heteroaryloxy” refers to the group -O-heteroaryl, where the group is attached to the parent molecular structure via the oxygen. Non-limiting examples of heteroaryl groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizynyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Non-limiting examples of heteroaryl rings containing
- 25 a single ring are: 1,2,3,4-tetrazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, triazinyl, thiazolyl, 1*H*-imidazolyl, oxazolyl, furanyl, thiophenyl, pyrimidinyl, 2-phenylpyrimidinyl, pyridinyl, 3-methylpyridinyl, and 4-dimethylaminopyridinyl. Non-limiting examples of heteroaryl rings containing 2 or more fused rings include: benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, cinnolinyl, naphthyridinyl, phenanthridinyl, 7*H*-purinyl, 9*H*-purinyl, 6-amino-9*H*-purinyl, 5*H*-pyrrolo[3,2-*d*]pyrimidinyl, 7*H*-pyrrolo[2,3-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, 2-phenylbenzo[*d*]thiazolyl, 1*H*-
- 30 indolyl, 4,5,6,7-tetrahydro-1-*H*-indolyl, quinoxalinyl, 5-methylquinoxalinyl, quinazolinyl, quinolinyl, 8-hydroxy-quinolinyl, 1*H*-benzo[*d*]imidazol-2(3*H*)-inyl, 1*H*-benzo[*d*]imidazolyl, and isoquinolinyl.

One non-limiting example of a heteroaryl group as described above is C₁-C₅ heteroaryl, which has 1 to 5 carbon ring atoms and at least one additional ring atom that is a heteroatom (for example, 1 to 4 additional ring atoms that are heteroatoms) independently selected from nitrogen (N), oxygen (O), or sulfur (S). Examples of C₁-C₅ heteroaryl include, but are not limited to, triazinyl, thiazol-2-yl, thiazol-4-yl, imidazol-1-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, isoxazolin-5-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

[0102] *Heteroarylalkyl*: The term “heteroarylalkyl” refers to an -(alkylene)-heteroaryl radical where heteroaryl and alkylene are as disclosed herein and which are optionally substituted by one or more of the exemplary substituent groups described herein. The “heteroarylalkyl” group is bonded to the parent molecular structure through the alkylene moiety. The term “heteroarylalkoxy” refers to an -O-[heteroarylalkyl] radical (-O-[(alkylene)-heteroaryl]), which is attached to the parent molecular structure through the oxygen.

[0103] *Heterocycloalkyl*: The term “heterocycloalkyl” or “heterocyclyl” as used herein, is a non-aromatic ring wherein at least one atom is a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus, and the remaining atoms are carbon, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments, a “heterocycloalkyl” or “heterocyclyl” refers to groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocycle group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (*e.g.*, C₁-C₆-heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as “C₁-C₆-heterocycle” refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. In some embodiments, it is understood that the heterocycle ring has additional heteroatoms in the ring. Designations such as “4-6-membered heterocycle” refer to the total number of atoms that are contained in the ring (*i.e.*, a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In some embodiments, in heterocycles that have two or more heteroatoms, those two or more heteroatoms are the same or different from one another. In some embodiments, heterocycles are optionally substituted. In some embodiments, binding to a heterocycle is at a heteroatom or via a carbon atom (*i.e.*, in some embodiments, the foregoing groups, as derived from the groups listed above, are C-attached or N-attached where such is possible). Examples of heterocycloalkyl groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2*H*-pyranyl, 4*H*-pyranyl, dioxanyl, 1,3-dioxolanyl,

pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. In embodiments, heterocyclic moieties having a single ring include: diazirinyl, aziridinyl, urazolyl, azetidyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl oxathiazolidinonyl, oxazolidinonyl, hydantoinyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl, piperidin-2-onyl (valerolactam), 2,3,4,5-tetrahydro-1*H*-azepinyl, 2,3-dihydro-1*H*-indole, and 1,2,3,4-tetrahydroquinoline. Non-limiting examples of heterocyclic moieties having 2 or more rings include: hexahydro-1*H*-pyrrolizinyl, 3a,4,5,6,7,7a-hexahydro-1*H*-benzo[d]imidazolyl, 3a,4,5,6,7,7a-hexahydro-1*H*-indolyl, 1,2,3,4-tetrahydroquinolyl, chromanyl, isochromanyl, indolyl, isoindolyl, and decahydro-1*H*-cycloocta[b]pyrrolyl. The heterocycloalkyl group can be substituted or unsubstituted. The heterocycle groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. In some embodiments, depending on the structure, a heterocycle group is a monoradical or a diradical (*i.e.*, a heterocyclene group). The heterocycles described herein are substituted or unsubstituted. In embodiments, a heterocycle is substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, nitro, amino, and amido moieties.

[0104] *Moiety*: The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0105] *Nitro*: The term “nitro” refers to a -NO_2 group.

[0106] *Phosphoryl*: The term “phosphoryl” refers to a -P(=O)(R')_2 , or -P(=O)(R')- group, where R' is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon or through the heteroatom), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon) group, unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring.

[0107] *Sulfonamide*: The term “sulfonamide” or sulfonamido” refers to the following groups: $\text{-S(=O)}_2\text{-(R')}_2$, $\text{-N(R')-S(=O)}_2\text{-R'}$, $\text{-S(=O)}_2\text{-N(R')-}$, or $\text{-N(R')-S(=O)}_2\text{-}$, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring.

[0108] *Sulfonyl*: The term “sulfonyl” refers to a $-S(=O)_2R'$, or $-S(=O)_2-$ group, where R' is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), amino, cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein. For example, in one embodiment, the sulfonyl group is $-SO_2R'$, where R' is alkyl substituted with a carbonyl group.

[0109] *Sulfinyl*: The term “sulfinyl” refers to a chemical moiety with formula $-S(=O)R'$, $-S(=O)-$, or $-S(=O)(=NR')$, where R' is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein.

[0110] *Ureido*: The term “ureido” refers to a chemical moiety with formula $-NR'C(O)NR'$, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring.

[0111] Whenever a term (*e.g.*, alkyl or aryl) or either of their prefix roots (*e.g.*, alk- or ar-) appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, affixing the suffix “-ene” to a group indicates the group is a divalent moiety, *e.g.*, arylene is the divalent moiety of aryl, heteroarylene is the divalent moiety of heteroaryl, cycloalkylene is the divalent moiety of cycloalkyl, heterocycloalkylene is the divalent moiety of heterocycloalkyl, or heterocyclylene is the divalent moiety of heterocyclyl. Similarly, affixing the suffix “-oxy” to a group indicates the group is attached to the parent molecular structure through an oxygen atom ($-O-$) (*e.g.*, cycloalkyloxy, benzyloxy, and the like).

[0112] The term “substituted” is used throughout the specification. The term “substituted” is defined herein as a moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several (*e.g.*, 1 to 10) substituents as defined herein below and wherein said replacement is with a permissible substituent, *e.g.*, a substituent which upon substitution for the hydrogen results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. The term “optionally substituted” means that the specified group is unsubstituted or substituted by one or more substituents. The substituents are capable of replacing one or two hydrogen atoms of a single moiety at a time. Thus, where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. In addition, these substituents can replace two

hydrogen atoms on two adjacent carbons to form said substituent, new moiety or unit. For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two-hydrogen atom replacement includes carbonyl, oximino, and the like. A two-hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. The term "substituted" is used throughout the present specification to indicate that a moiety can have one or more of the hydrogen atoms replaced by a substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, difluoromethyl is a substituted C₁ alkyl; trifluoromethyl is a substituted C₁ alkyl; 4-hydroxyphenyl is a substituted aromatic ring; (N,N-dimethyl-5-amino)octanyl is a substituted C₈ alkyl; 3-guanidinopropyl is a substituted C₃ alkyl; and 2-carboxypyridinyl is a substituted heteroaryl.

[0113] A wide variety of substituents are well known, and methods for their formation and introduction into a variety of parent groups are also well known. Representative substituents include but are not limited to alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, arylalkyl, alkylaryl, aryl, heteroaryl, heterocycloalkyl, hydroxyalkyl, arylalkyl, aminoalkyl, haloalkyl, thioalkyl, alkylthioalkyl, carboxyalkyl, imidazolylalkyl, indolylalkyl, mono-, di- and trihaloalkyl, mono-, di- and trihaloalkoxy, aminoalkylamino, dialkylamino, alkoxy, hydroxy, halo (*e.g.*, —Cl and —Br), nitro, oximino, —COOR⁵⁰, —COR⁵⁰, —SO_{0.2}R⁵⁰, —SO₂NR⁵⁰R⁵¹, —NR⁵²SO₂R⁵⁰, =C(R⁵⁰R⁵¹), =N—OR⁵⁰, =N—CN, =C(halo)₂, =S, =O, —CON(R⁵⁰R⁵¹), —OCOR⁵⁰, —OCON(R⁵⁰R⁵¹), —N(R⁵²)CO(R⁵⁰), —N(R⁵²)COOR⁵⁰, —N(R⁵²)CON(R⁵⁰R⁵¹), —P(OR⁵⁰)₂, —P(O)R⁵⁰R⁵¹, and —P(O)OR⁵⁰OR⁵¹, wherein R⁵⁰, R⁵¹ and R⁵² may be independently selected from the following: a hydrogen atom and a branched or straight-chain, C₁₋₆ alkyl, C₃₋₆-cycloalkyl, C₄₋₆-heterocycloalkyl, heteroaryl and aryl group, with or without substituents. When permissible, R⁵⁰ and R⁵¹ can be joined together to form a carbocyclic or heterocyclic ring system.

[0114] The following are still further non-limiting examples of substituents which can substitute for hydrogen atoms on a moiety: halogen (chlorine (Cl), bromine (Br), fluorine (F) and iodine(I)), —CN, —NO₂, oxo (=O), —OR', —SR', —N(R')₂, —NR'C(O)R', —SO₂R', —SO₂OR', —SO₂N(R')₂, —C(O)R', —C(O)OR', —C(O)N(R')₂, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₂-C₈ alkenyl, C₂-C₈ alkynyl, C₃-C₁₄ cycloalkyl, aryl, heterocycle, or heteroaryl, wherein each of the alkyl, haloalkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heterocycle, and heteroaryl groups is optionally substituted with 1-10 (*e.g.*, 1-6 or 1-4) groups selected independently from halogen, —CN, —NO₂, oxo, and R'; wherein R', at each occurrence, independently is hydrogen, —OR'', —SR'', —C(O)R'', —C(O)OR'', —C(O)N(R'')₂, —SO₂R'', S(O)₂OR'', —N(R'')₂, —NR''C(O)R'', C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, cycloalkyl (*e.g.*, C₃-C₆ cycloalkyl), aryl, heterocycle, or heteroaryl, or two R' units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle has 3 to 7 ring atoms; wherein R'', at each occurrence, independently is hydrogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl, cycloalkyl

(*e.g.*, C₃-C₆ cycloalkyl), aryl, heterocycle, or heteroaryl, or two R''' units taken together with the atom(s) to which they are bound form an optionally substituted carbocycle or heterocycle wherein said carbocycle or heterocycle has, for example, 3 to 7 ring atoms.

[0115] In embodiments, a substituent is selected from halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR', and -SO₂R', wherein each instance of R' independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In certain embodiments thereof, R' independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is unsubstituted C₁-C₃ alkyl.

10 [0116] In some embodiments, the substituents are selected from:

- i) -OR'''; for example, -OH, -OCH₃, -OCH₂CH₃, -OCH₂CH₂CH₃;
- ii) -C(O)R'''; for example, -COCH₃, -COCH₂CH₃, -COCH₂CH₂CH₃;
- iii) -C(O)OR'''; for example, -CO₂CH₃, -CO₂CH₂CH₃, -CO₂CH₂CH₂CH₃;
- iv) -C(O)N(R'')₂; for example, -CONH₂, -CONHCH₃, -CON(CH₃)₂;
- 15 v) -N(R'')₂; for example, -NH₂, -NHCH₃, -N(CH₃)₂, -NH(CH₂CH₃);
- vi) halogen: -F, -Cl, -Br, and -I;
- vii) -CH_eX_g; wherein X is halogen, m is from 0 to 2, e+g =3; for example, -CH₂F, -CHF₂, -CF₃, -CCl₃, or -CBr₃;
- viii) -SO₂R'''; for example, -SO₂H; -SO₂CH₃; -SO₂C₆H₅;
- 20 ix) C₁-C₆ linear, branched, or cyclic alkyl;
- x) Cyano
- xi) Nitro;
- xii) N(R''')C(O)R''';
- xiii) Oxo (=O);
- 25 xiv) Heterocycle; and
- xv) Heteroaryl.

wherein each R''' is independently hydrogen, optionally substituted C₁-C₆ linear or branched alkyl (*e.g.*, optionally substituted C₁-C₄ linear or branched alkyl), or optionally substituted C₃-C₆ cycloalkyl (*e.g.*, optionally substituted C₃-C₄ cycloalkyl); or two R''' units can be taken together to form a ring comprising 3-7 ring atoms. In certain aspects, each R''' is independently hydrogen, C₁-C₆ linear or branched alkyl optionally substituted with halogen or C₃-C₆ cycloalkyl or C₃-C₆ cycloalkyl.

[0117] At various places in the present specification, substituents of compounds are disclosed in groups or in ranges. It is specifically intended that the description include each and every individual subcombination of the members of such groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose C₁, C₂, C₃, C₄, C₅, C₆, C₁-C₆, C₁-C₅, C₁-C₄, C₁-C₃, C₁-C₂,
5 C₂-C₆, C₂-C₅, C₂-C₄, C₂-C₃, C₃-C₆, C₃-C₅, C₃-C₄, C₄-C₆, C₄-C₅, and C₅-C₆ alkyl.

[0118] Unless otherwise noted, when two substituents are taken together to form a ring having a specified number of ring atoms (*e.g.*, R² and R³ taken together with the nitrogen (N) to which they are attached to form a ring having from 3 to 7 ring members), the ring can have carbon atoms and optionally one or more (*e.g.*, 1 to 3) additional heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). The ring can be saturated or partially saturated and can be optionally substituted.
10

[0119] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence (*e.g.*, in N(R⁹)₂, each R⁹ may be the same or different than the other). Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.
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[0120] Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a
20 racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (*i.e.*, cis and trans isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to embrace hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

[0121] Compounds described herein can comprise an asymmetric atom (also referred as a chiral center), and some of the compounds can comprise one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers. The present teachings and compounds disclosed herein include such enantiomers and diastereomers, as well as the racemic and resolved, enantiomerically pure R and S stereoisomers, as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers can be obtained in pure form
30 by standard procedures known to those skilled in the art, which include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. The present teachings also encompass cis and trans isomers of compounds containing alkenyl moieties (*e.g.*, alkenes and imines). It is also understood that the present teachings encompass all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled
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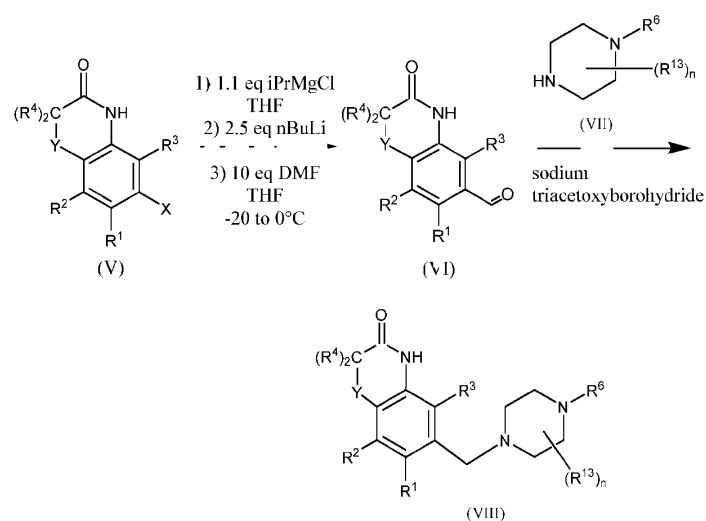
in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

General Techniques

[0122] Standard chemical laboratory techniques are used to implement the synthetic methods disclosed herein. The exemplary synthetic methods described in the Examples of the disclosure can be used to prepare still other compounds disclosed herein.

Processes

[0123] In an aspect, the present disclosure provides a process for the synthesis of the compound of formula (VIII) summarized below under the reaction conditions disclosed herein:



[0124] wherein:

X is Br or I,

Y is C, NH, NR^5 , O or S,

each of R^1 through R^6 and R^{13} is independently H, F, methyl, $\text{C}_2\text{-C}_8$ alkyl that is saturated or unsaturated, $\text{C}_3\text{-C}_8$ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or $\text{C}_3\text{-C}_8$ aryl or heteroaryl, $-\text{CO}_2\text{H}$, $-\text{CONHR}^{15}$, $-\text{CONH}_2$,

or independently any two of R^1 through R^5 and any two R^{13} may form a $\text{C}_3\text{-C}_8$ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a $\text{C}_3\text{-C}_8$ aryl or heteroaryl,

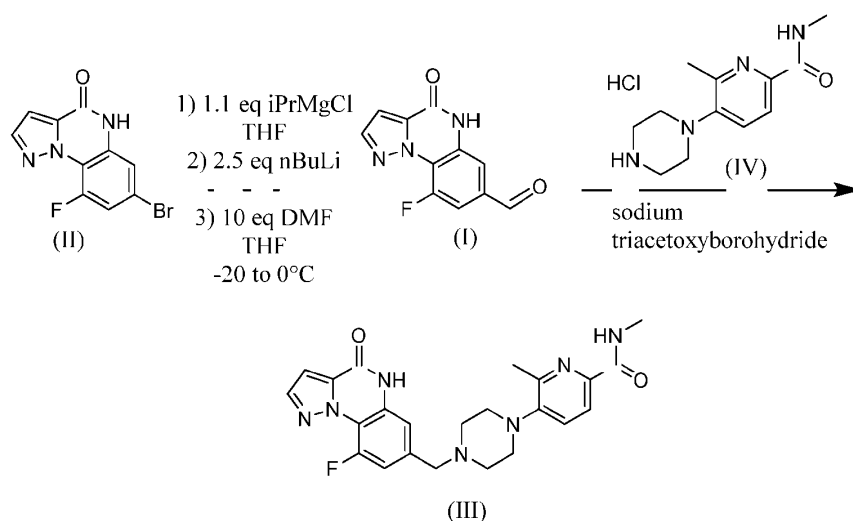
or independently any two of R^1 through R^5 and any two R^{13} may form a $\text{C}_5\text{-C}_{10}$ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R^{15} ,

and each of R^1 through R^6 and R^{13} independently is optionally substituted with R^{15} ,
 n is from 0 to 8, and

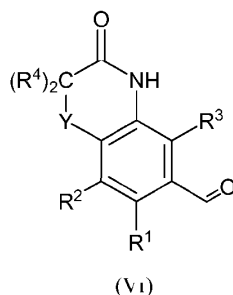
each R^{15} is independently selected from cyano, amino, nitro, C_1 - C_{10} alkyl, C_2 - C_{10}
 alkenyl, C_2 - C_{10} alkynyl, saturated or unsaturated cycloalkyl, saturated or unsatu-
 5 rated heterocyclyl, aryl, and heteroaryl, and

wherein each of R^1 through R^6 and R^{13} and R^{15} , including any ring or rings they
 may form, independently optionally comprises at least one group selected from -
 $C(O)$ -, $-C(O)O$ -, $-C(O)NH$ -, $-C(O)N<$ -, $-N<$ -, $-NH$ -, $-N=$ -, $-O$ -, $-S$ -, $-S(O)$ -, and -
 SO_2 -.

- 10 **[0125]** In an aspect, the present disclosure provides a process for preparing the compound of
 formula (III) as summarized below:



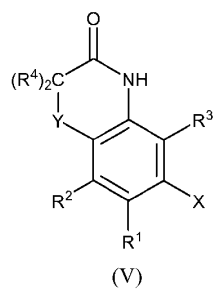
- [0126]** In an aspect, the present disclosure provides a process for preparing a compound of
 formula (VI):



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comprising the steps of:

- (i) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



- (ii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- 5 (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- 10 (vi) maintaining the mixture for 5 minutes to overnight e.g. about 20 minutes at about -10°C to -40°C, e.g. at -20°C to -40°C ;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours e.g. 10 minutes;
- 15 (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) warming the mixture of step (viii) to room temperature over about 2 hours,
- (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- 20 (xi) optionally purifying the product,
- wherein:
- X is Br or I,
- Y is C, NH, NR⁵, O or S,
- 25 each of R¹ through R⁵ is independently H, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl,

or independently any two of R^1 through R^5 may form a C_3 - C_8 cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C_3 - C_8 aryl or heteroaryl,

or independently any two of R^1 through R^5 may form a C_5 - C_{10} bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R^{15} ,

and each of R^1 through R^5 independently may be substituted with R^{15} ,

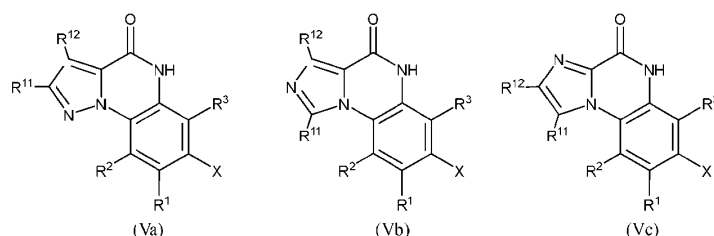
and

each R^{15} is independently selected from cyano, amino, nitro, C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, C_2 - C_{10} alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocycloalkyl, aryl, and heteroaryl, and

[0127] wherein each of R^1 through R^5 and R^{15} , including any ring or rings they may form, independently optionally comprises at least one group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

[0128] In some embodiments of the process for preparing a compound of formula (VIII) provided herein, Y is C. In some embodiments, Y is NH. In some embodiments, Y is NR^5 . In some embodiments, Y is O. In some embodiments, Y is S.

[0129] In some embodiments, Y, R^4 and R^5 are defined such that the compound of formula (V) has the structure (Va), (Vb) or (Vc):



wherein R^{11} and R^{12} are each independently H, F, methyl, C_2 - C_8 alkyl that is saturated or unsaturated, C_3 - C_8 cycloalkyl or heterocycloalkyl that is saturated or unsaturated, C_3 - C_8 aryl or heteroaryl, $-CO_2H$, $-CONHR^{15}$, or $-CONH_2$,

and each of R^{11} and R^{12} independently is optionally substituted with R^{15} .

[0130] In some embodiments, the compound of formula (V) has the structure (Va). In some embodiments, the compound of formula (V) has the structure (Vb). In some embodiments, the compound of formula (V) has the structure (Vc).

[0131] In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is Br or X is I, and all R groups present are H. In some embodiments, X is Br or X is I, R^2 is F, and R^1 and R^3 through R^5 and R^{15} are H. In some embodiments, X is Br or X is I, and none of

R^1 through R^5 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

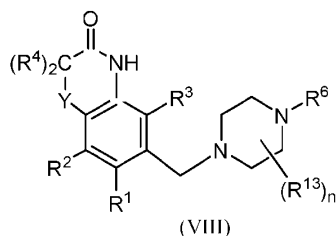
[0132] In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, R^2 is F, and R^1 , R^3 and R^{15} are H. In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, and none of R^1 , R^3 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

[0133] In some embodiments, the process includes the step of adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C following step (vi). In some embodiments, the reaction temperature is maintained at -25°C , for 5 minutes to 3 hours e.g. for 10 minutes, 30 minutes or one hour. In some embodiments, the process does not include the step of adding 0.25 to 1 equivalent additional *n*-BuLi.

[0134] In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

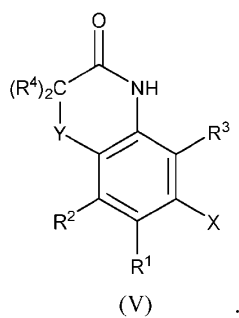
[0135] In some embodiments, the process includes the step of purifying the product at step (xi). In some embodiments, the process does not include the step of purifying the product at step (xi).

[0136] In another aspect, the present disclosure provides a process for preparing a compound of formula (VIII):

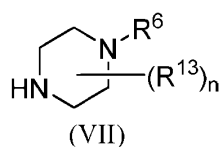


wherein the process comprises the steps of:

(xvi) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



- (xvii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- (xviii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (xix) cooling the mixture of step (iii) to -20°C;
- 5 (xx) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (xxi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour,
10 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (xxii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- (xxiii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while
15 maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (xxiv) warming the mixture of step (viii) to room temperature over about 2 hours,
- (xxv) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
20
- (xxvi) optionally purifying the product,
- (xxvii) combining the product of step (xi) with 1 equivalent of a compound of formula (VII):



, or a salt thereof,

- 25 in about 50 volumes, relative to the compound of formula (V) on a volume-to-mass basis, of a solvent selected from 2-methyl-tetrahydrofuran (2-MeTHF), dichloromethane (DCM), dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), isopropyl acetate (IPAc), dimethylacetamide (DMAc), isopropyl alcohol (IPA), ethanol (EtOH), tetrahydrofuran (THF), dimethylformamide (DMF), ethyl acetate (EtOAc),
30 and acetonitrile (MeCN), for example THF, and about 4 equivalents of acetic acid;
- (xxviii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;

(xxix) adding 2 to 3 equivalents of sodium triacetoxyborohydride ((CH₃COO)₃BHNa) and stirring overnight at about 20°C to about 25°C; and

(xxx) optionally purifying the product,

wherein:

5 X is Br or I,

Y is C, NH, NR⁵, O or S,

each of R¹ through R⁶ and R¹³ is independently H, F, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl, -CO₂H, -CONHR¹⁵, -CONH₂,

10 or independently any two of R¹ through R⁵ and any two R¹³ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl,

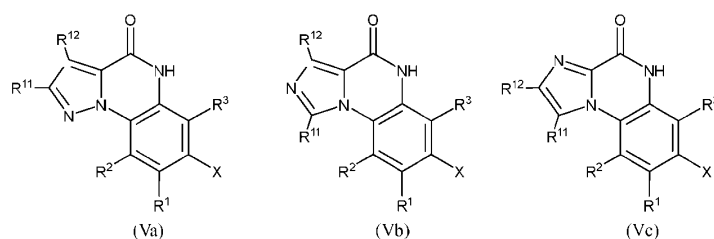
or independently any two of R¹ through R⁵ and any two R¹³ may form a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

15 and each of R¹ through R⁶ and R¹³ independently is optionally substituted with R¹⁵,
n is from 0 to 8, and

each R₁₅ is independently selected from cyano, amino, nitro, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocyclyl, aryl, and heteroaryl, and

20 wherein each of R¹ through R⁶ and R¹³ and R¹⁵, including any ring or rings they may form, independently optionally comprises at least one group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

25 **[0137]** In some embodiments of the process for preparing a compound of formula (VIII) provided herein, Y is C. In some embodiments, Y is NH. In some embodiments, Y is NR⁵. In some embodiments, Y is O. In some embodiments, Y is S. In some embodiments, Y, R⁴ and R⁵ are defined such that the compound of formula (V) has the structure (Va), (Vb) or (Vc):



wherein R^{11} and R^{12} are each independently H, F, methyl, C_2 - C_8 alkyl that is saturated or unsaturated, C_3 - C_8 cycloalkyl or heterocycloalkyl that is saturated or unsaturated, C_3 - C_8 aryl or heteroaryl, $-CO_2H$, $-CONHR^{15}$, or $-CONH_2$,
and each of R^{11} and R^{12} independently is optionally substituted with R^{15} .

5 [0138] In some embodiments, the compound of formula (V) has the structure (Va). In some embodiments, the compound of formula (V) has the structure (Vb). In some embodiments, the compound of formula (V) has the structure (Vc).

[0139] In some embodiments, X is Br. In some embodiments, X is I. In some embodiments, X is Br or X is I, and all R groups present are H. In some embodiments, X is Br or X is I, R^2 is F,
10 and R^1 and R^3 through R^5 and R^{15} are H. In some embodiments, X is Br or X is I, and none of R^1 through R^5 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

[0140] In some embodiments in which the compound of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, R^2 is F, and R^1 , R^3 and R^{15} are H. In some embodiments in which the compound
15 of formula (V) is (Va), (Vb) or (Vc), X is Br or X is I, and none of R^1 , R^3 and R^{15} comprise a group selected from $-C(O)-$, $-C(O)O-$, $-C(O)NH-$, $-C(O)N<$, $-N<$, $-NH-$, $-N=$, $-O-$, $-S-$, $-S(O)-$, and $-SO_2-$.

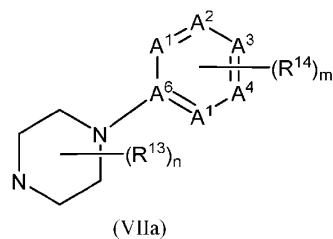
[0141] In some embodiments, the process includes the step of adding 0.25 to 1 equivalent additional n-BuLi and maintaining the reaction temperature at $-25^\circ C$ following step (vi). In some
20 embodiments, the reaction temperature is maintained at $-25^\circ C$, for 5 minutes to 3 hours e.g. for 10 minutes, 30 minutes or one hour. In some embodiments, the process does not include the step of adding 0.25 to 1 equivalent additional n-BuLi.

[0142] In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

[0143] In some embodiments, the process includes the step of purifying the product at step
25 (xi). In some embodiments, the process does not include the step of purifying the product at step (xi).

[0144] In some embodiments, the free base (VII) is used in step (xii). In some embodiments, a salt of the free base (VII) is used, e.g. the hydrochloride salt of (VII).

[0145] In some embodiments of the process for preparing a compound of formula (VIII) pro-
30 vided herein, the compound of structure (VIIa) is used:



, or a salt thereof,

[0146] wherein:

[0147] each of A¹, A², A³, A⁴, A⁵ and A⁶ is independently selected from N and C,

[0148] m=0 to 5,

5 [0149] wherein each R¹⁴ is independently H, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl,

[0150] or independently any two R¹⁴ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl, or independently any two R¹⁴ may form
10 a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

[0151] each R¹⁴ independently may be substituted with R¹⁵,

[0152] each R¹⁴ (including any ring or rings they may form) independently optionally comprises at least one group selected from -C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-,
15 , -N=, -O-, -S-, -S(O)-, and -SO₂-,

[0153] and R¹³, n and R¹⁵ are as defined herein.

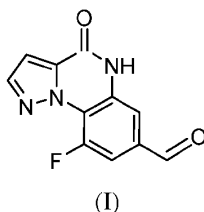
[0154] In some embodiments, m and n are both 0. In some embodiments, n is 0 and m is selected from 1, 2, 3, 4 and 5. In some embodiments, n is 0 and m is 1. In some embodiments, n is 0, m is 1 and R¹⁴ is unsubstituted and is methyl or C₂-C₈ alkyl that is saturated or unsaturated,
20 C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl.

[0155] In some embodiments, 0, 1, 2, 3, or 4 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remainder are C. In some embodiments, any 1 of A¹, A², A³, A⁴, A⁵ and A⁶ is N and the remaining 5 are C. In some embodiments, any 2 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 4
25 are C. In some embodiments, any 3 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 3 are C. In some embodiments, any 4 of A¹, A², A³, A⁴, A⁵ and A⁶ are N and the remaining 2 are C.

[0156] In some embodiments, the free base form of (VIIa) is used. In some embodiments, a salt form of (VIIa) is used, e.g. the hydrochloride salt.

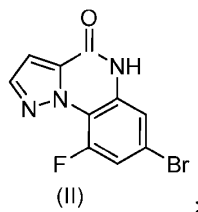
[0157] In some embodiments, the product of step (x) is purified. In some embodiments, in step (v), the internal reaction temperature is maintained below -20°C . In some embodiments, in step (vi), the internal reaction temperature is maintained below -20°C . In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

- 5 [0158] In a further aspect, the present disclosure provides a process for preparing a compound of formula of (I):



comprising the steps of:

- 10 (xii) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)



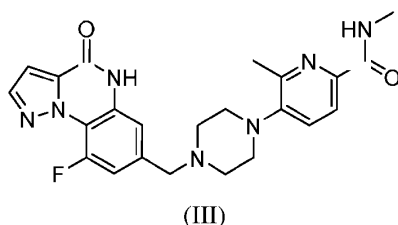
- (xiii) cooling the mixture of (II) in THF to between 0°C and -10°C ;
- (xiv) adding 1 to 2 equivalents of isopropylmagnesium chloride ($(\text{CH}_3)_2\text{MgCl}$) to the cooled mixture of step (ii) to obtain a second mixture;
- 15 (xv) cooling the mixture of step (iii) to -20°C ;
- (xvi) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; $\text{CH}_3(\text{CH}_2)_3\text{Li}$), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C , e.g. at -20°C to -40°C ;
- 20 (xvii) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C , e.g. at -20°C to -40°C ;
- (xviii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C , optionally for 5 minutes to 3 hours, ;
- 25 (xix) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; $(\text{CH}_3)_2\text{NCHO}$) in dry THF to the mixture of step (vii) to obtain a new mixture while

maintaining the mixture's temperature below -20°C , then permitting the reaction to warm to -5°C to 0°C ;

- (xx) permitting the temperature to warm to room temperature over about 2 hours,
- (xxi) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xxii) optionally purifying the product.

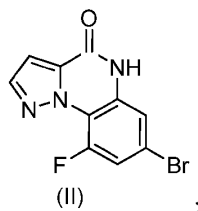
[0159] In some embodiments, in step (v), the internal reaction temperature is maintained below -20°C . In some embodiments, in step (vi), the internal reaction temperature is maintained below -20°C . In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

- 10 [0160] In a further aspect, the present disclosure provides is a process for preparing 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one (III):



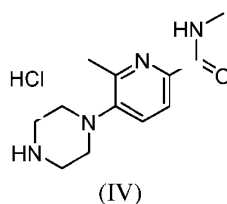
- 15 comprising the steps of:

- (i) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)



- (ii) cooling the mixture of (II) in THF to between 0°C and -10°C ;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ($(\text{CH}_3)_2\text{MgCl}$) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C ;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; $\text{CH}_3(\text{CH}_2)_3\text{Li}$), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C , e.g. at -20°C to -40°C ;

- (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide ((CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) permitting the temperature to warm to room temperature over about 2 hours,
- (x) adding about 1/50 volume of water to quench the reaction;
- (xi) optionally purifying the product;
- (xii) combining the product of step (xi) with 1 equivalent of N,6-dimethyl-5-(piperazin-1-yl)picolinamide hydrochloride having a formula of (IV):



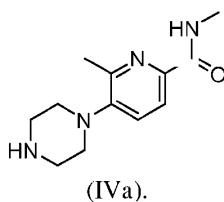
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in about 50 volumes of a solvent selected from THF, DMF, EtOAc, and MeCN, for example THF, and about 4 equivalents of acetic acid;

- (xiii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;
- (xiv) adding 2 to 3 equivalents of sodium triacetoxyborohydride and stirring overnight at about 20°C to about 25°C; and
- (xv) optionally purifying the product.

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[0161] In some embodiments, the free base form of (IV) is used, referred to herein as (IVa):



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[0162] In some embodiments, a salt of (IVa) is used other than the hydrochloride salt, e.g. the HBr salt of (IVa).

[0163] In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

[0164] In some embodiments, in step (v), the internal reaction temperature is maintained below -20° C. In some embodiments, in step (vi), the internal reaction temperature is maintained below -20° C. In some embodiments, in step (viii), 4 equivalents of dry DMF is added.

[0165] In an embodiment, a compound of formula (III) is prepared from a compound of formula (II) as described herein according to the following procedure.

[0166] To an oven dried, 100 mL 3 neck round-bottom flask (RBF) equipped with a stir bar and internal temperature probe are added: the compound of formula (II) (1g, 3.55 mmol) and dry THF (30mL) (less than 200 ppm H₂O). The milky suspension is cooled to -10-0°C before adding iPrMgCl (2M, 1.95mL, 3.9 mmol) dropwise, then stirred for ~35 mins (e.g. 25 minutes to 50 minutes, e.g. 35 minutes). A heterogenous, beige/yellow mixture is obtained. The mixture is cooled to about -20°C (e.g. -20°C) before *n*-BuLi (1.6M in hexanes, 4.43mL, 7.09 mmol) is added dropwise over 5-10 mins. Internal reaction temperature is maintained below -20°C (e.g. below -20°C and not colder than -40°C). The mixture is aged for 20 minutes below -20°C (e.g. below -20°C and not colder than -40°C). A heterogenous, yellow mixture is obtained. A sample is taken and analyzed by LCMS after an aliquot is diluted in water/acetonitrile (ACN). About 76.61% lithiation is observed (or, for example, 70%-85% or 75%-80% or 76%-77% lithiation) with 23.39% (or, for example, 15%-30% or 20-25% or 23%-24%) compound of formula (II) remaining. An additional 0.5 eq *n*-BuLi is added (1.1 mL). The mixture is maintained at the same temperature for 10 mins (or, for example, 5 minutes to 1 hour). Reaction temperature is maintained at -25°C. A sample is taken and analyzed by LCMS after aliquot diluted in water/acetonitrile (ACN). About 98.5% lithiation is observed (e.g. 98.5% or 95-99%) with 1.5% SM remaining. Dry DMF (2.75 mL, 35.5mmol, containing e.g. less than 200 ppm water) in 10 mL dry THF (containing e.g. less than 200 ppm water) is added while the temp is below -20°C. The reaction is allowed to warm to -5°C to 0°C. The reaction is allowed to warm to room temperature (e.g. 18°C to 27°C, e.g. 20°C-25°C) over 2 hours, and then quenched with 1 mL water. The reaction mixture is concentrated onto ~10 g silica gel for normal phase purification using a 40 g column and gradient elution using 0-50-100% EA/Hex. Product containing fractions are combined and concentrated to dryness, then left on high vac overnight to provide the compound of formula (I) (820mg, 65% yield).

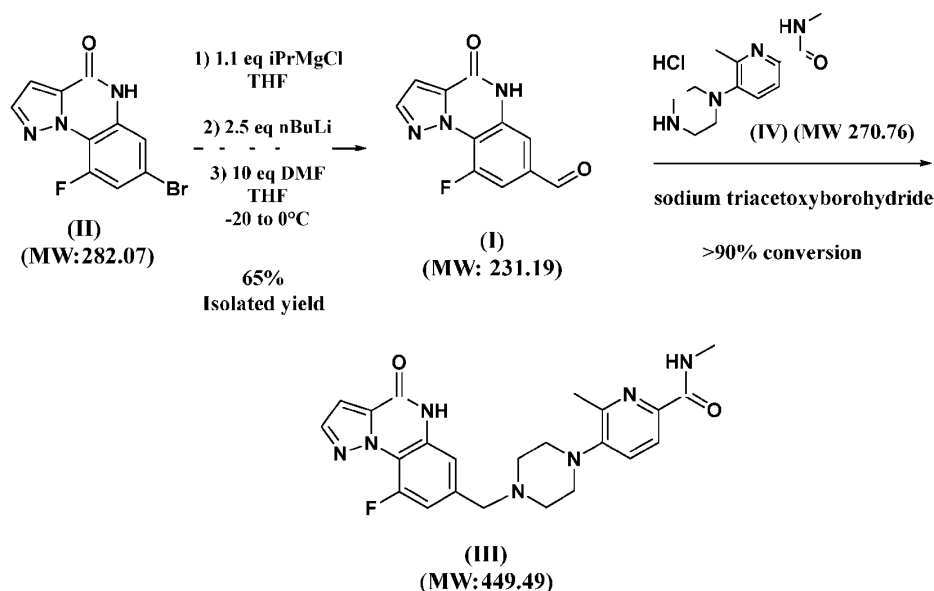
[0167] Step 2:

[0168] A mixture of (I) (10mg), (IV) (1 eq), solvent (50 volumes), AcOH (4 equivalents) are stirred in a vial for ~75 mins (e.g. 45-90 minutes, 60-80 minutes, or 75 minutes) at room temperature (e.g. 18°C to 27°C, e.g. 20°C-25°C). 2 to 3 equivalents of sodium triacetylborohydride (STAB) is then added and the resulting mixture was stirred for overnight (e.g. 8-24 hours, 12-20 hours, 15 hours) at room temperature (e.g. 18°C to 27°C, e.g. 20°C-25°C). The reaction is sampled and analyzed by LC.

EXAMPLES

Example 1.

[0169] An example of the synthetic procedure as disclosed herein is disclosed and described below. A diagram of the exemplary synthetic procedure follows.

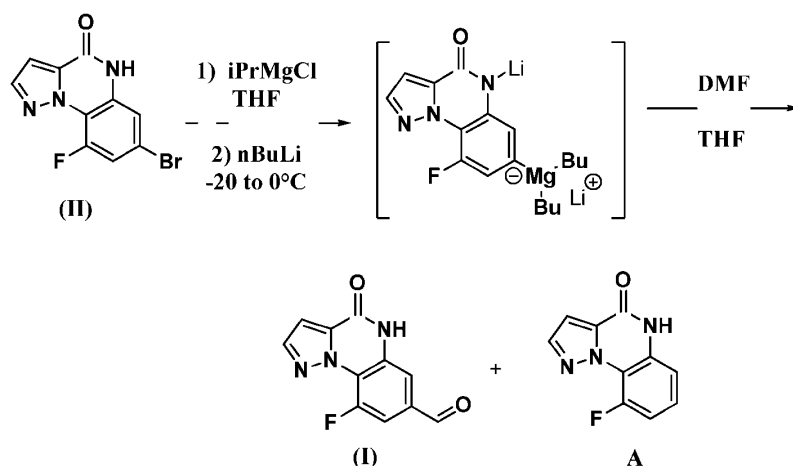


[0170] The compounds of formulae (II) and (IV) may be prepared, for example, as described in WO2023025307, the relevant parts of which are incorporated herein in their entirety.

[0171] A synthetic route to the compound of formula (III) was developed that employs the compounds of formulae (II) and (IV). This route to the compound of formula (III) does not use Stille Coupling, which includes the use of palladium and organic stannane.

[0172] Development of Preparation of (I) from (II): Formylation via Metal-Halogen Exchange.

[0173] A challenge in the preparation of (I) from (II) ("Step 1") stems from the presence of an acid N-H bond in the compound of formula (II), which can quench the Grignard or organo-lithium reagents needed for the metal-halogen exchange. It was discovered that the combined use of a Grignard and butyl lithium can overcome this issue.



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Preparation of (I) from (II) with Proposed Intermediate

[0174] Through careful screening, it was found that the stoichiometry of the Grignard did not directly impact the conversion of the Step 1 reaction. For example, protonated byproduct A, the quenched form of the proposed lithiated intermediate, was not formed after 1.0, 1.25 or 1.5 equivalents of *i*-PrMgCl was charged, which suggested that the Grignard alone was not able to enable metal-halogen exchange (Table 1).

[0175] When 2 equivalents of *n*-butyl lithium were charged after the addition of *i*-PrMgCl, the protonated byproduct A was found in the reaction samples quenched by water. This indicates the formation of metalated species via metal-halogen exchange at the aryl-bromide bond. A possible structure of the metalated (lithiated) intermediate hypothesized to occur between (II) and (I) is shown in the above diagram of the preparation of (I) from (II) with proposed intermediate.

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Table 1 Preparation of (I) from (II) with Varying Amounts of *i*-PrMgCl

Sample point:	% Area (relative)								
	1 eq <i>i</i> -PrMgCl			1.25 eq <i>i</i> -PrMgCl			1.5 eq <i>i</i> -PrMgCl		
	(II)	A	(I)	(II)	A	(I)	(II)	A	(I)
After addition of <i>i</i> -PrMgCl	100	0	0	100	0	0	100	0	0
After 2 eq <i>n</i> -BuLi	27.75	72.25	0	25.97	74.03	0	33.52	66.48	0
After 1 eq DMF	33.94	30.76	31.14	25.6	37.46	34.85	31.11	31.68	31.01
After quench	47.26	8.2	37.74	35.66	20.03	33.7	48.71	14.61	33.17

[0176] Complete metal-halogen exchange was observed when more than 2.5 equivalents of *n*-butyl lithium was used in combination with *i*-PrMgCl, as shown in Table 2. Full conversion (>99%) of the starting material (II) to the lithiated intermediate, which was detected in the form of the quenched product A, was observed when 2.5 equivalents of *n*-butyl lithium was charged after the *i*-PrMgCl addition. However, the interception of the metalated intermediate with 1 equivalent of DMF only resulted in 20-30% conversion to the desired aldehyde product, the compound of formula (I) (Table 2).

Table 2. Preparation of (I) from (II) with Varying Amounts of *n*-Butyl Lithium

Sample point:	% Area (relative)								
	2.0 eq <i>n</i> -BuLi			2.5 eq <i>n</i> -BuLi			3.0 eq <i>n</i> -BuLi		
	(II)	A	(I)	(II)	A	(I)	(II)	A	(I)
After <i>i</i> -PrMgCl and <i>n</i> -BuLi addition	9.42	90.58	0	1.13	98.87	0	0.33	99.67	0
After 1 eq DMF	7.95	71.23	20.82	0.52	66.61	32.88	0	78.91	21.09
After quench	9.85	60.54	29.61	0	67.13	32.87	0	81.01	18.99

[0177] The conversion of the metalated intermediate to aldehyde (I) was significantly improved by increasing the amount of DMF, as shown in Table 3. When more than 2.0 equivalents of DMF was used, the protonated byproduct A was reduced to <20% from 66% and the desired product (I) was formed in >68%.

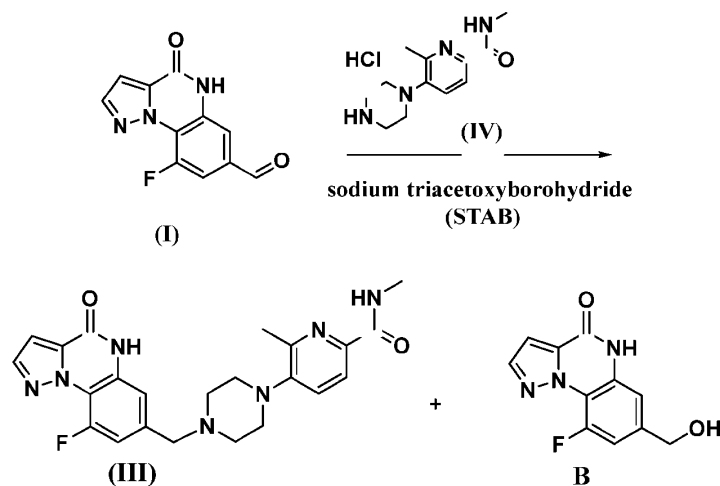
Table 3. Preparation of (I) from (II) with Varying Amounts of DMF

	% Area (relative)	
	1.0 eq DMF	2.0 eq DMF

Sample point:	(II)	A	(I)	(II)	A	(I)
After 1 eq <i>i</i> -PrMgCl, 2.5 eq <i>n</i> -BuLi	9.27	90.73	0	22.00	78.00	0
After DMF addition	5.22	69.04	25.74	18.96	27.48	53.56
After quench, 0°C	2.28	66.3	31.42	18.48	13.35	68.17
After quench, 20°C	2.85	82.13	15.03	29.86	10.08	60.06

Table 3 (cont'd).

Sample point:	% Area (relative)					
	4.0 eq DMF			10.0 eq DMF		
	(II)	A	(I)	(II)	A	(I)
After 1 eq <i>i</i> -PrMgCl, 2.5 eq <i>n</i> -BuLi	19.87	80.13	0	22.37	77.63	0
After DMF addition	16.31	21.77	61.93	19.71	14.89	65.40
After quench, 0°C	17.15	7.57	75.27	13.32	6.93	73.75
After quench, 20°C	26.45	7.88	65.68	33.78	5.2	61.02

Optimization of Preparation of (III) from (I): Reductive Amination

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[0178] The optimization of this step (“Step 2”) focused on reagent stoichiometry and solvents. It was found that combination of 2 eq AcOH and 3 equivalents sodium triacetoxyborohydride (STAB) gave the highest conversion (91%) in DCE (dichloroethane). Use of water scavengers such as $\text{Ti}(\text{O}i\text{-Pr})_4$ did not provide improved conversion (Table 4).

Table 4 Step 2 Optimization

Conditions: RT in DCE	% Area (relative)				
	(I)	(IV)	(III)	B	Conversion

A - 1 eq AcOH, 2eq STAB + 1 eq STAB	19.1	37.9	27.8	7.4	59%
	11.7	27.7	46.0	8.1–80%	
C - 2 eq AcOH, 2eq STAB + 1 eq STAB	11.2	25.0	47.3	7.2	81%
	6.8	8.0	67.2	8.7–91%	
E - 3 eq AcOH, 2eq STAB + 1 eq STAB	13.8	38.8	31.6	8.3	70%
	10.8	16.6	54.0	10.1–83%	
G - 4 eq AcOH, 2eq STAB + 1 eq STAB	15.1	23.0	43.0	7.5	74%
	10.1	4.6	66.1	8.9–87%	
B - 1 eq AcOH, 2eq STAB + 1 eq Ti(Oi-Pr) ₄	21.9	48.2	12.4	10.7–36%	
D - 2 eq AcOH, 2eq STAB + 1 eq Ti(Oi-Pr) ₄	25.9	47.5	10.4	9.7–29%	
F - 3 eq AcOH, 2eq STAB + 1 eq Ti(Oi-Pr) ₄	25.6	45.4	10.9	11.1–30%	
H - 4 eq AcOH, 2eq STAB + 1 eq Ti(Oi-Pr) ₄	24.6	52.8	7.4	10.0	23%

[0179] While DCE was an effective solvent in the initial screening, it is not deemed as a viable solvent for scale up due to its toxicity. A solvent screening was carried out to find out a more process friendly choice. To this end, THF gave >93% conversion with only a small amount of reduced alcohol product B. In DMF the reaction reached full conversion, but a significant amount of reduction byproduct B was formed (Table 5).

Table 5 Optimization of Step 2 Solvent

Conditions: 2 eq AcOH, 3eq STAB, RT	% Area (relative)				
Solvent	(I)	(IV)	(III)	B	Conversion
THF	4.9	12.86	62.77	16.16	93%
DMF	0.01	18.86	45.16	33.29	100%
EtOAc	32.38	43.77	8.82	7.96	21%
MeCN	21.72	43.83	19.21	10.3	47%
IPA	36.14	51.32	2.37	4.36	6%
MeOH	35.98	55.44	0.33	2.74	1%

Example 2.

[0180] Preparation of (I) from (II):

- 10 [0181] To an oven dried, 100 mL 3 neck RBF equipped with a stir bar and internal temperature probe was added: (II) (1g, 3.55 mmol) and dry THF (30mL). The milky suspension was cooled to -10-0°C before adding iPrMgCl (2M, 1.95mL, 3.9 mmol) dropwise, then stirred for ~35 mins. A heterogenous, beige/yellow mixture was observed. The mixture was cooled to ~

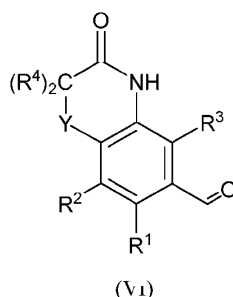
-20°C before *n*-BuLi (1.6M in hexanes, 4.43mL, 7.09 mmol) was added dropwise over 5-10 mins. Internal reaction temperature was maintained below -20°C. The mixture was aged for 20 mins below -20°C. A heterogenous, yellow mixture was observed. A sample was taken and analyzed by LCMS after aliquot diluted in water/ACN. About 76.61% lithiation, detected
5 in the form of protonated byproduct A, was observed (FIG. 3A, larger peak; see also MS data of FIG. 3B), with 23.39% (II) remaining (FIG. 3A, smaller peak; see also FIGs. 3B-3C). An additional 0.5 eq *n*-BuLi was added (1.1 mL). Aged for 10 mins. Reaction temperature maintained at -25°C. A sample was taken and analyzed by LCMS after aliquot diluted in water/ACN. About 98.5% lithiation observed, 1.5% SM remaining. See FIGs. 3D-3F. Dry DMF
10 (2.75 mL, 35.5 mmol) in 10 mL dry THF was added while the temperature was below -20°C. The reaction was allowed to warm to -5 to 0°C. The reaction was allowed to warm to room temperature over 2 hrs, and then quenched with 1 mL water. The reaction mixture was concentrated onto ~10 g silica gel for normal phase purification using a 40 g column and gradient elution using 0-50-100% EA/Hex. Product containing fractions were combined and concentrated to dryness, then left on high vac overnight to provide (I) (820mg, 65% yield).
15

[0182] Preparation of (III) from (I):

[0183] A mixture of (I) (10mg), (IV) (1 eq), solvent (50 volumes), AcOH (~4 eq) were stirred in a vial for ~75 mins at room temperature. 2 to 3 equivalents of STAB was then added and the resulting mixture was stirred for overnight at RT. The reaction was sampled
20 and analyzed by LCMS. See FIGs. 3G-3I. The compound of formula (III) was obtained.

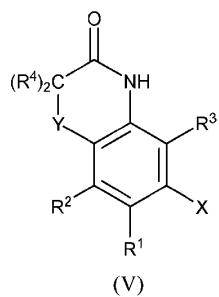
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula (VI):



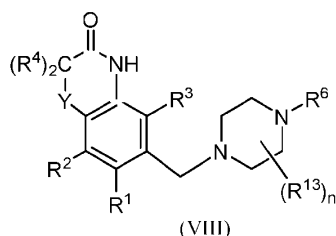
- 5 comprising the steps of:

- (i) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



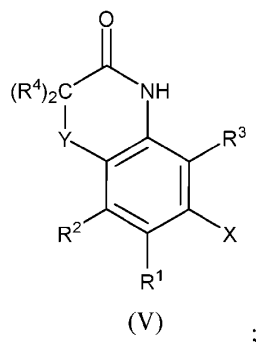
- (ii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- 10 (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at
- 15 about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vi) maintaining the mixture for 5 minutes to overnight e.g. about 20 minutes at about -10°C to -40°C, e.g. at -20°C to -40°C ;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours e.g. 10 minutes;

- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; $(\text{CH}_3)_2\text{NCHO}$) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C , then permitting the reaction to warm to -5°C to 0°C ;
- 5 (ix) warming the mixture of step (viii) to room temperature over about 2 hours,
- (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xi) optionally purifying the product,
- wherein:
- 10 X is Br or I,
- Y is C, NH, NR^5 , O or S,
- each of R^1 through R^5 is independently H, methyl, $\text{C}_2\text{-C}_8$ alkyl that is saturated or unsaturated, $\text{C}_3\text{-C}_8$ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or $\text{C}_3\text{-C}_8$ aryl or heteroaryl,
- 15 or independently any two of R^1 through R^5 may form a $\text{C}_3\text{-C}_8$ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a $\text{C}_3\text{-C}_8$ aryl or heteroaryl,
- or independently any two of R^1 through R^5 may form a $\text{C}_5\text{-C}_{10}$ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R^{15} ,
- 20 and each of R^1 through R^5 independently may be substituted with R^{15} ,
- and
- each R^{15} is independently selected from cyano, amino, nitro, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ alkenyl, $\text{C}_2\text{-C}_{10}$ alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocycloalkyl, aryl, and heteroaryl, and
- 25 wherein each of R^1 through R^5 and R^{15} , including any ring or rings they may form, independently optionally comprises at least one group selected from $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{C}(\text{O})\text{NH}-$, $-\text{C}(\text{O})\text{N}<$, $-\text{N}<$, $-\text{NH}-$, $-\text{N}=\text{}$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, and $-\text{SO}_2-$.
2. A process for preparing a compound of formula (VIII):

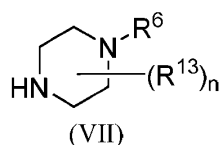


wherein the process comprises the steps of:

- (i) providing a first mixture of a compound of formula (V) in dry tetrahydrofuran (THF):



- (ii) cooling the mixture of (V) in THF to between 0°C and -10°C;
- 5 (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to
- 10 obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- 15 (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours;
- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to
- 20 warm to -5°C to 0°C;
- (ix) warming the mixture of step (viii) to room temperature over about 2 hours,
- (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xi) optionally purifying the product,
- 25 (xii) combining the product of step (xi) with 1 equivalent of a compound of formula (VII):



, or a salt thereof,

in about 50 volumes, relative to the compound of formula (V) on a volume-to-mass basis, of a solvent selected from 2-methyl-tetrahydrofuran (2-MeTHF), dichloromethane (DCM), dimethylsulfoxide (DMSO), N-methyl-2-pyrrolidone (NMP), isopropyl acetate (IPAc), dimethylacetamide (DMAc), isopropyl alcohol (IPA), ethanol (EtOH), tetrahydrofuran (THF), dimethylformamide (DMF), ethyl acetate (EtOAc), and acetonitrile (MeCN), and about 4 equivalents of acetic acid;

(xiii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;

(xiv) adding 2 to 3 equivalents of sodium triacetoxyborohydride ((CH₃COO)₃BHNa) and stirring overnight at about 20°C to about 25°C; and

(xv) optionally purifying the product,

wherein:

X is Br or I,

Y is C, NH, NR⁵, O or S,

each of R¹ through R⁶ and R¹³ is independently H, F, methyl, C₂-C₈ alkyl that is saturated or unsaturated, C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated, or C₃-C₈ aryl or heteroaryl, -CO₂H, -CONHR¹⁵, -CONH₂, or independently any two of R¹ through R⁵ and any two R¹³ may form a C₃-C₈ cycloalkyl or heterocycloalkyl that is saturated or unsaturated or a C₃-C₈ aryl or heteroaryl,

or independently any two of R¹ through R⁵ and any two R¹³ may form a C₅-C₁₀ bicycloalkyl or heterobicycloalkyl that is saturated, unsaturated or aromatic and independently that is unsubstituted or substituted with R¹⁵,

and each of R¹ through R⁶ and R¹³ independently is optionally substituted with R¹⁵,

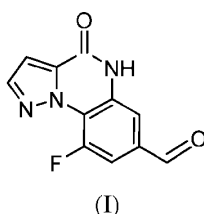
n is from 0 to 8, and

each R₁₅ is independently selected from cyano, amino, nitro, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, saturated or unsaturated cycloalkyl, saturated or unsaturated heterocyclyl, aryl, and heteroaryl, and

wherein each of R¹ through R⁶ and R¹³ and R¹⁵, including any ring or rings they may form, independently optionally comprises at least one group selected from –

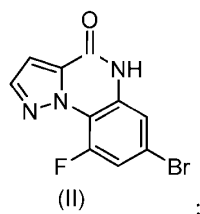
C(O)-, -C(O)O-, -C(O)NH-, -C(O)N<, -N<, -NH-, -N=, -O-, -S-, -S(O)-, and -SO₂-.

3. The process of claim 2, wherein, in step (xii), the product of step (xi) is combined with 1 equivalent of a compound of formula (VII) or a salt thereof in about 50 volumes, relative to the compound of formula (V) on a volume-to-mass basis, tetrahydrofuran (THF).
4. The process of claim 1 or 2, wherein, in step (v), the internal reaction temperature is maintained below -20° C.
5. The process of claim 1 or 2, wherein, in step (vi), the internal reaction temperature is maintained below -20° C.
6. The process of claim 1 or 2, wherein, in step (viii), 4 equivalents of dry DMF is added.
7. A process for preparing a compound of formula of (I):



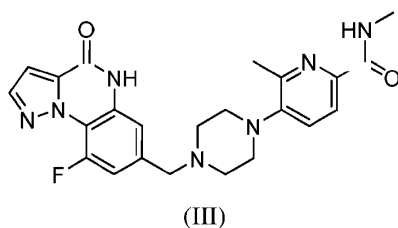
comprising the steps of:

- (i) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)



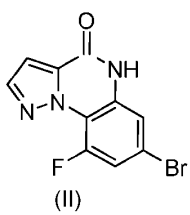
- (ii) cooling the mixture of (II) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;
- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C ;

- (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C ;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours, ;
- (viii) adding between about 2 and 10 equivalents of dry dimethylformamide (DMF; (CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) permitting the temperature to warm to room temperature over about 2 hours,
- (x) adding water to quench the reaction e.g. a volume of water in the range of 1/50 volume to 20 volumes e.g. 0.5 volumes to 20 volumes; and
- (xi) optionally purifying the product.
8. A process for preparing 7-((4-(2-methyl-6-(methylcarbamoyl)pyridin-3-yl)piperazin-1-yl)methyl)-9-fluoropyrazolo[1,5-a]quinoxalin-4(5H)-one having a formula of (III):

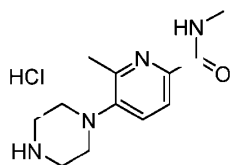


comprising the steps of:

- (i) providing a first mixture of a compound of formula (II) in dry tetrahydrofuran (THF)
- (ii) cooling the mixture of (II) in THF to between 0°C and -10°C;
- (iii) adding 1 to 2 equivalents of isopropylmagnesium chloride ((CH₃)₂MgCl) to the cooled mixture of step (ii) to obtain a second mixture;
- (iv) cooling the mixture of step (iii) to -20°C;



- (v) adding 1.5 to 3 equivalents *n*-butyllithium (*n*-BuLi; CH₃(CH₂)₃Li), optionally as a solution in hexanes, heptanes, or a combination of the two, to the cooled mixture of step (iv) to obtain a third mixture while maintaining the internal reaction temperature at about -10°C to -40°C, e.g. at -20°C to -40°C;
- 5 (vi) maintaining the mixture for 5 minutes to 24 hours, e.g. 5 minutes, 20 minutes, 1 hour, 6 hours, 9 hours, 12 hours, 15 hours, 18 hours, 24 hours at about -10°C to -40°C, e.g. at -20°C to -40°C;
- (vii) optionally adding 0.25 to 1 equivalent additional *n*-BuLi and maintaining the reaction temperature at -25°C, optionally for 5 minutes to 3 hours,;
- 10 (viii) adding between about 2 and 10 equivalents of dry dimethylformamide ((CH₃)₂NCHO) in dry THF to the mixture of step (vii) to obtain a new mixture while maintaining the mixture's temperature below -20°C, then permitting the reaction to warm to -5°C to 0°C;
- (ix) permitting the temperature to warm to room temperature over about 2 hours,
- 15 (x) adding about 1/50 volume of water to quench the reaction;
- (xi) optionally purifying the product;
- (xii) combining the product of step (xi) with 1 equivalent of N,6-dimethyl-5-(piperazin-1-yl)picolinamide hydrochloride having a formula of (IV):



(IV)

- 20 in about 50 volumes, relative to the compound of formula (V) on a volume-to-mass basis, of a solvent selected from THF, DMF, EtOAc, and MeCN, and about 4 equivalents of acetic acid;
- (xiii) stirring the mixture of step (xii) at room temperature for about 1 to 2 hours;
- 25 (xiv) adding 2 to 3 equivalents of sodium triacetoxyborohydride and stirring overnight at about 20°C to about 25°C; and
- (xv) optionally purifying the product.
9. The process of claim 8, wherein, in step (xii), the product of step (xi) is combined with 1 equivalent of a compound of formula (IV) in about 50 volumes, relative to the compound of
- 30 formula (V) on a volume-to-mass basis, of tetrahydrofuran (THF).

10. The process of claim 7 or 8, wherein, in step (v), the internal reaction temperature is maintained below -20° C.
11. The process of claim 7 or 8, wherein, in step (vi), the internal reaction temperature is maintained below -20° C.
- 5 12. The process of claim 7 or 8, wherein, in step (viii), 4 equivalents of dry DMF is added.