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(54) Title: INHIBITING UBIQUITIN SPECIFIC PEPTIDASE 9X

(57) Abstract: The disclosure provides novel chemical compounds useful as inhibitors of ubiquitin specific peptidase 9X (USP9X). USP9X inhibiting compounds are useful in the treatment of disease and disorders associated with modulation of USP9X, such as cancer.



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INHIBITING UBIQUITIN SPECIFIC PEPTIDASE 9X

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Patent Application No. 62/784,981, filed December 26, 2018, which is hereby incorporated herein by reference in its entirety.

TECHNICAL FIELD

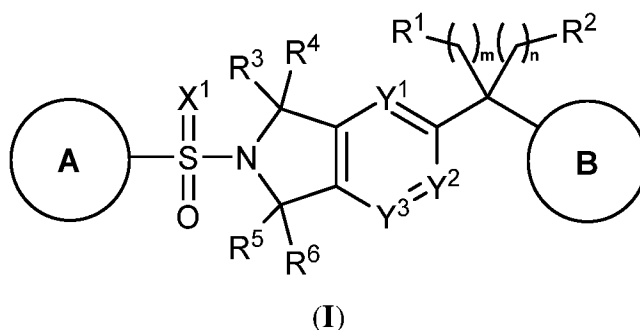
[0002] This disclosure relates to novel chemical compositions for inhibiting ubiquitin specific peptidase 9X.

BACKGROUND

[0003] Deubiquitylating enzymes (DUBs) control a number of cellular processes, including the stability and function of a variety of oncoproteins, by reversing ubiquitination. Ubiquitin specific peptidase 9X (USP9X) is a member of the USP family of DUBs and is a key regulator of protein homeostasis for protein substrates including several that are known to be important in cancer. These include oncogenic or protumorigenic proteins and proteins involved in the anti-tumor immune response. These proteins can be important in tumor cells, immune cells, or other cells, such as stromal cells that play a role in cancer. Examples include MCL-1, survivin, ITCH, and CEP55. Overexpression and/or mutation of DUBs and their substrates have been correlated with cancer initiation and progression. USP9X has been suggested to be a negative prognostic factor for several oncology indications and may be associated with decreased overall survival in some cancer types (e.g., esophageal squamous cell carcinoma, non-small cell lung cancer, and multiple myeloma). Targeting USP9X can enhance an anti-tumor immune response through regulation of key maintenance proteins. Therefore, USP9X is a target for cancer drug development, particularly as a means to deplete oncoprotein substrates that have been labeled undruggable and/or through activation of the immune response. There is a need for compounds that inhibit USP9X and are useful for treating diseases and disorders associated with modulation of USP9X.

SUMMARY

[0004] One embodiment of this disclosure relates to compounds of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is NR or O;

Y^1 is CR^7 or N;

Y^2 is CR^8 or N;

Y^3 is CR^9 or N;

wherein the heteroaryl formed when at least one of Y^1 , Y^2 , or Y^3 is N may comprise an N-oxide;

Ring A is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring A is optionally substituted with one or more R^a ;

each R^a is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclcyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R^a group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

Ring B is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring B is optionally substituted with one or more R^b ;

each R^b is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R^b group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R^1 and R^2 are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

or R^1 and R^2 combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R^1 and R^2 group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₈cycloalkyl, and optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

or R^3 and R^4 , or R^5 and R^6 , or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R³, R⁴, R⁵, and R⁶ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆ aliphatic;

R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, and optionally substituted C₁-C₆aliphatic,

wherein an optionally substituted R⁷, R⁸, and R⁹ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R group may be optionally substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

each R' is independently selected from the group consisting of optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R' group may be substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

m is 0, 1, or 2; and

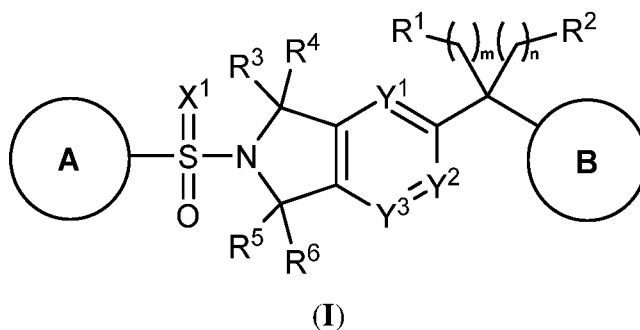
n is 0, 1, or 2.

[0005] Another aspect of this invention relates to compounds of Formula I that are USP9X Inhibitors. Unless otherwise indicated, a "USP9X Inhibitor" as used herein refers to a compound of Formula I having one or more of the following characteristics when tested in the Biochemical Assay of Example 3: (i) an IC₅₀ value of ≤ 0.1 μM and > 0.001 μM; (ii) an IC₅₀ value of ≤ 1 μM and > 0.1

μM ; (iii) an IC_{50} value of $\leq 10 \mu\text{M}$ and $> 1 \mu\text{M}$; and (iv) an IC_{50} value of $\leq 25 \mu\text{M}$ and $> 10 \mu\text{M}$. In some embodiments, a USP9X Inhibitor is a compound of Formula I having an IC_{50} value of (i) an IC_{50} value of $\leq 0.1 \mu\text{M}$ and $> 0.001 \mu\text{M}$; (ii) an IC_{50} value of $\leq 1 \mu\text{M}$ and $> 0.1 \mu\text{M}$; or (iii) an IC_{50} value of $\leq 10 \mu\text{M}$ and $> 1 \mu\text{M}$ when tested in the Biochemical Assay of Example 3. In some embodiments, a USP9X Inhibitor is a compound of Formula I having an IC_{50} value of $\leq 0.1 \mu\text{M}$ and $> 0.001 \mu\text{M}$ when tested in the Biochemical Assay of Example 3. In some embodiments, a USP9X Inhibitor is a compound of Formula I having an IC_{50} value of $\leq 1 \mu\text{M}$ and $> 0.1 \mu\text{M}$ when tested in the Biochemical Assay of Example 3. In some embodiments, a USP9X Inhibitor is a compound of Formula I having an IC_{50} value $\leq 10 \mu\text{M}$ and $> 1 \mu\text{M}$ when tested in the Biochemical Assay of Example 3.

DETAILED DESCRIPTION

[0006] One aspect of this disclosure relates to compounds of Formula I:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, X^1 , Y^1 , Y^2 , Y^3 , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , m , and n are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0007] In some embodiments, compounds of Formula I are provided, wherein:

X^1 is O;

Y^1 is CR^7 or N;

Y^2 is CR^8 or N;

Y^3 is CR^9 or N;

wherein the heteroaryl formed when at least one of Y^1 , Y^2 , or Y^3 is N may comprise an N-oxide;

Ring A is:

(i) a monocyclic ring selected from C_3 - C_8 carbocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a ; or

- (ii) a bicyclic 9- to 12-membered ring comprising a phenyl ring,
wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and
wherein the bicyclic ring is optionally substituted with one or more R^a;
each R^a is independently selected from the group consisting of halogen, -OR, -NRC(O)R', optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,
wherein an optionally substituted R^a group may be substituted with one or more halogen;

Ring B is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl,
wherein the monocyclic ring is optionally substituted with one or more R^b; or
(ii) a bicyclic 9- to 12-membered ring comprising a phenyl ring,
wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and
wherein the bicyclic ring is optionally substituted with one or more R^b;
each R^b is independently selected from the group consisting of halogen, -OR, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,
wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of -NR₂ and C₁-C₆ aliphatic;
R¹ and R² are each independently selected from the group consisting of -H, -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic;
R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H and C₁-C₆aliphatic;
R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, -OR, and C₁-C₆aliphatic;

each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R group may be optionally substituted with one or more C₁-C₆aliphatic;

each R' is independently C₃-C₁₀cycloalkyl;

m is 0, 1, or 2; and

n is 0.

[0008] In some embodiments, compounds of Formula I are provided, wherein:

X¹ is O;

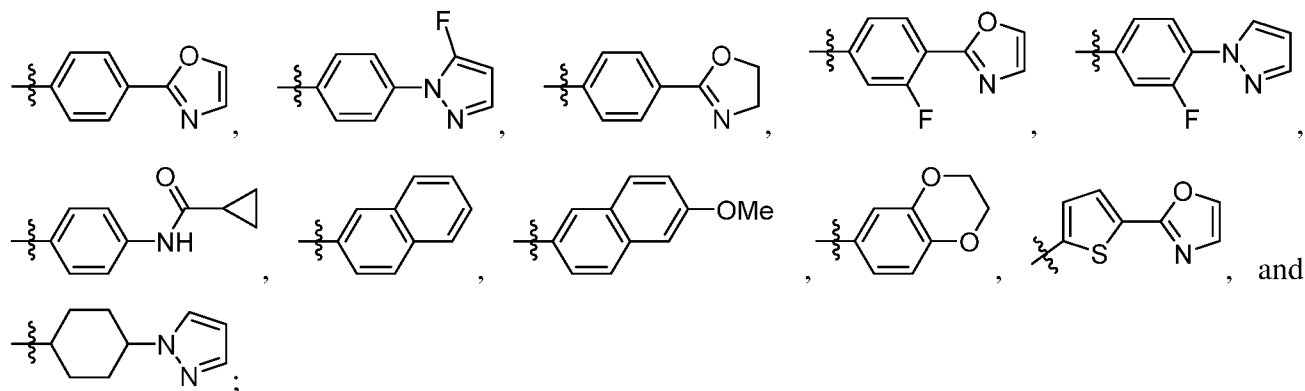
Y¹ is CR⁷ or N;

Y² is CR⁸ or N;

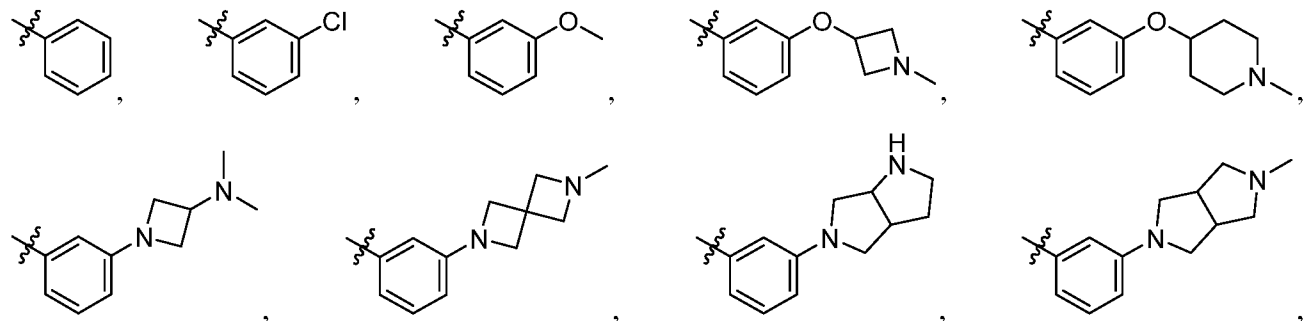
Y³ is CR⁹ or N;

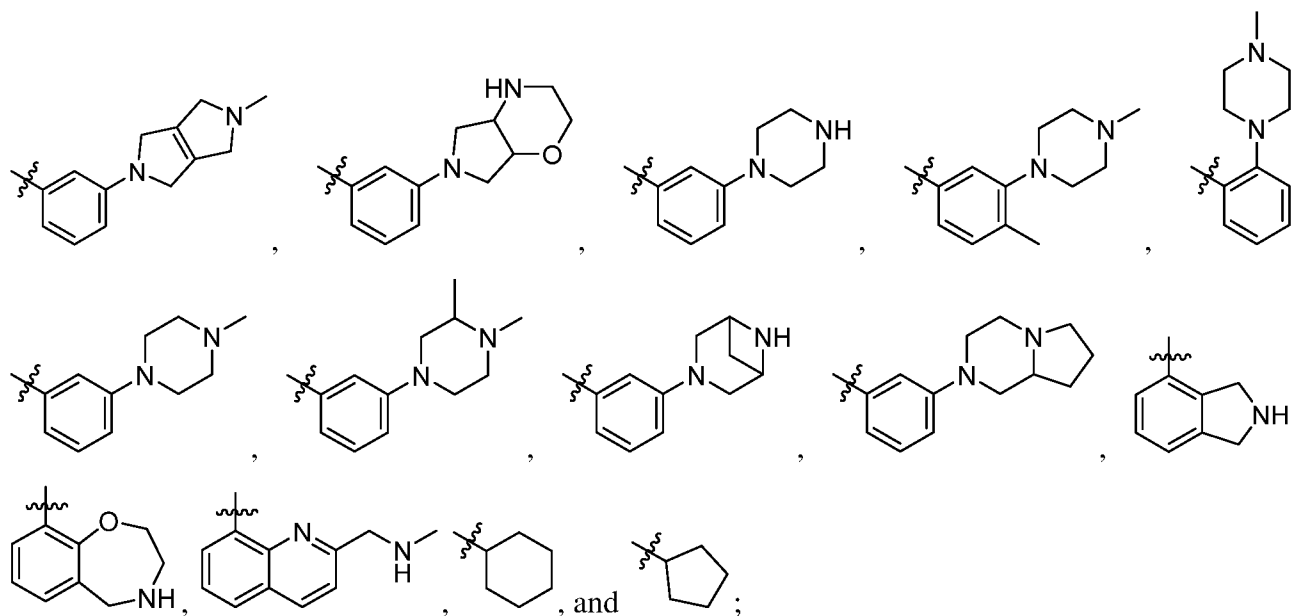
wherein the heteroaryl formed when at least one of Y¹, Y², or Y³ is N may comprise an N-oxide;

Ring A is selected from:



Ring B is selected from:





R¹ and R² are each independently selected from the group consisting of -H, -OH, -OMe, -NH₂, -NHMe, -CN, -C(O)NHMe, and methyl;

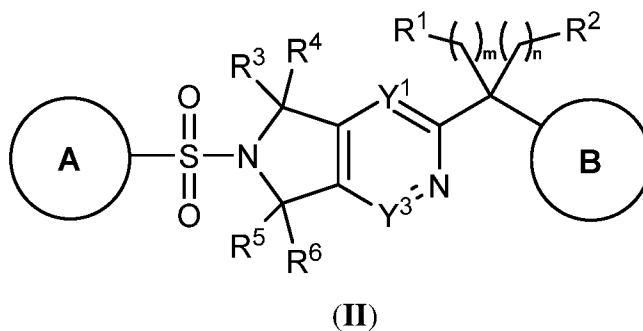
R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H and methyl;

R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, -OMe, and methyl;

m is 0, 1, or 2; and

n is 0.

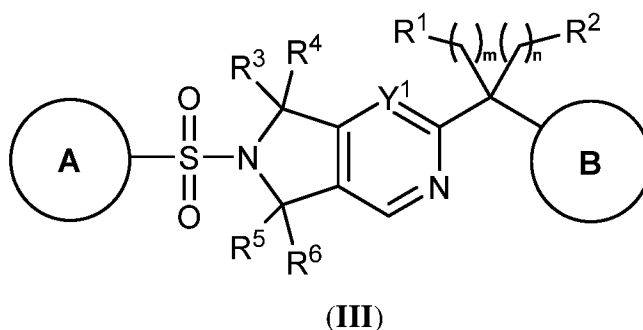
[0009] In some embodiments, this disclosure provides compounds of Formula II:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, Y¹, Y³, R¹, R², R³, R⁴, R⁵, R⁶, m, and n are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

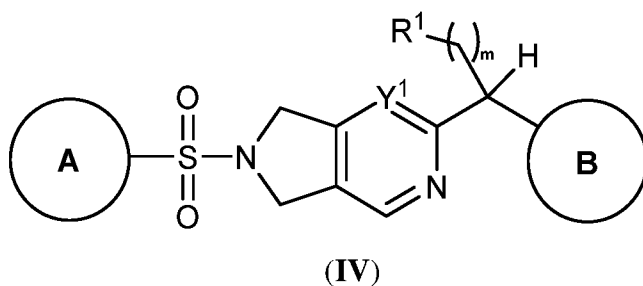
[0010] In some embodiments, this disclosure provides compounds of Formula III:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, Y¹, R¹, R², R³, R⁴, R⁵, R⁶, m, and n are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

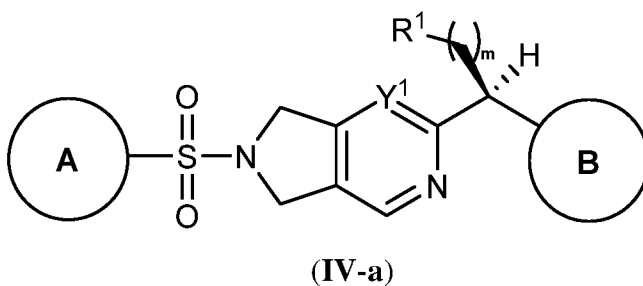
[0011] In some embodiments, this disclosure provides compounds of Formula IV:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, Y¹, R¹, and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

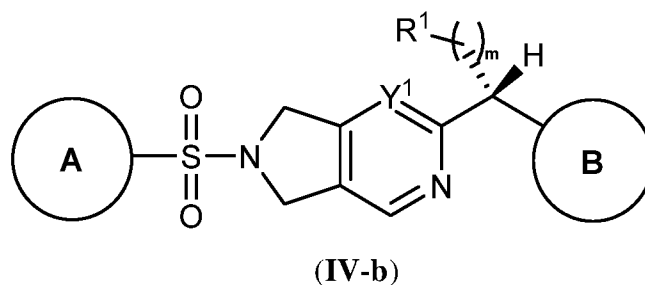
[0012] In some embodiments, this disclosure provides compounds of Formula IV-a:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, Y¹, R¹, and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

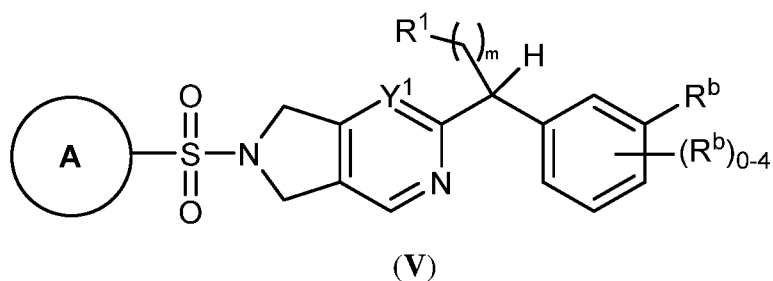
[0013] In some embodiments, this disclosure provides compounds of Formula IV-b:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Ring B, Y¹, R¹, and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

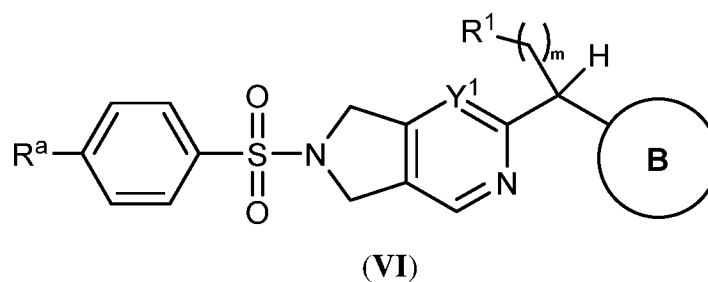
[0014] In some embodiments, this disclosure provides compounds of Formula V:



or a pharmaceutically acceptable salt thereof,

wherein Ring A, Y¹, R¹, R^b, and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

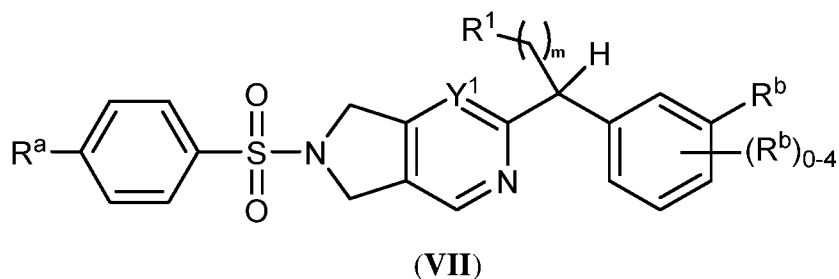
[0015] In some embodiments, this disclosure provides compounds of Formula VI:



or a pharmaceutically acceptable salt thereof,

wherein Ring B, Y¹, R¹, R^a, and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

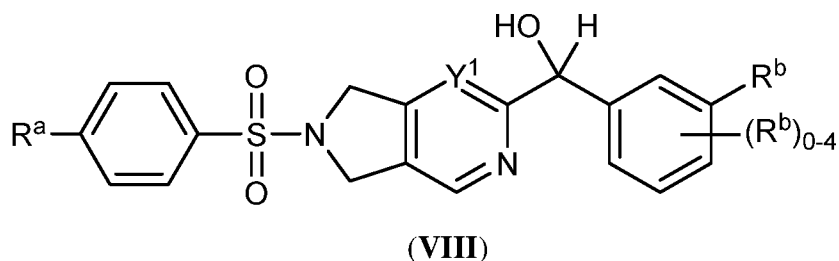
[0016] In some embodiments, this disclosure provides compounds of Formula VII:



or a pharmaceutically acceptable salt thereof,

wherein Y^1 , R^1 , R^a , R^b , and m are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

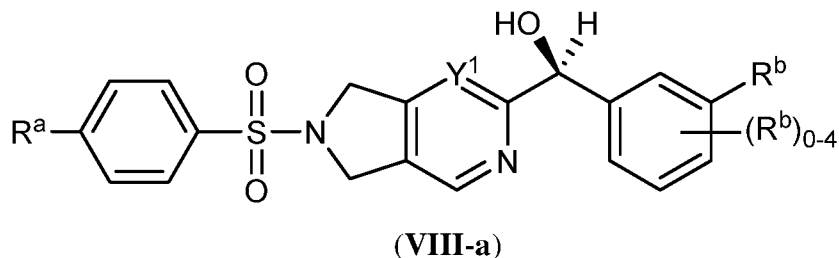
[0017] In some embodiments, this disclosure provides compounds of Formula VIII:



or a pharmaceutically acceptable salt thereof,

wherein Y^1 , R^a , and R^b are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

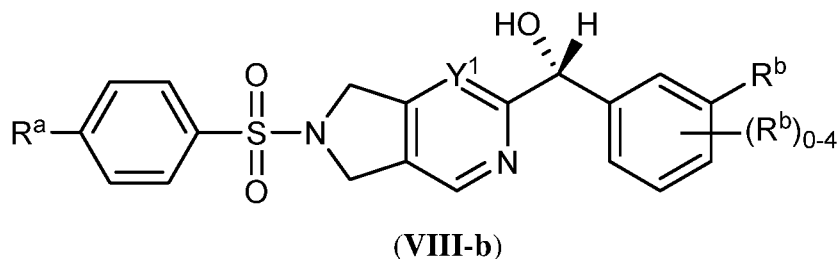
[0018] In some embodiments, this disclosure provides compounds of Formula VIII-a:



or a pharmaceutically acceptable salt thereof,

wherein Y^1 , R^a , and R^b are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0019] In some embodiments, this disclosure provides compounds of Formula VIII-b:



or a pharmaceutically acceptable salt thereof,

wherein Y^1 , R^a , and R^b are as defined above for Formula I and described in classes and subclasses herein, both singly and in combination.

[0020] In some embodiments of Formula I, X^1 is NR or O. In some embodiments, X^1 is NR. In some embodiments, X^1 is NH. In some embodiments, X^1 is O.

[0021] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, Y^1 is CR^7 or N. In some embodiments, Y^1 is CH or N. In some embodiments, Y^1 is CR^7 . In some embodiments, Y^1 is N. In some embodiments, Y^1 is CH.

[0022] In some embodiments of Formula I, Y^2 is CR^7 or N. In some embodiments, Y^2 is CH or N. In some embodiments, Y^2 is CR^7 . In some embodiments, Y^2 is N. In some embodiments, Y^2 is CH. In some embodiments, Y^2 is N and the resulting heteroaryl comprises an N-oxide.

[0023] In some embodiments of Formula I, Y^3 is CR^7 or N. In some embodiments, Y^3 is CH or N. In some embodiments, Y^3 is CR^7 . In some embodiments, Y^3 is N. In some embodiments, Y^3 is CH.

[0024] In some embodiments of Formula I, Y^1 is CR^7 , Y^2 is N, and Y^3 is CR^9 . In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is CR^9 . In some embodiments, Y^1 is CR^7 , Y^2 is N, and Y^3 is N. In some embodiments, Y^1 is CR^7 , Y^2 is CR^8 , and Y^3 is CR^9 . In some embodiments, Y^1 is CH, Y^2 is N, and Y^3 is CH. In some embodiments, Y^1 is N, Y^2 is N, and Y^3 is CH. In some embodiments, Y^1 is CH, Y^2 is N, and Y^3 is N. In some embodiments, Y^1 is CH, Y^2 is CH, and Y^3 is CH.

[0025] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring A is optionally substituted with one or more R^a .

[0026] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is:

(i) a monocyclic ring selected from C_3 - C_8 carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a ; or

(ii) a bicyclic 6- to 12-membered ring comprising a C_3 - C_{10} carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,

wherein the C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^a.

[0027] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a; or

(ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,

wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

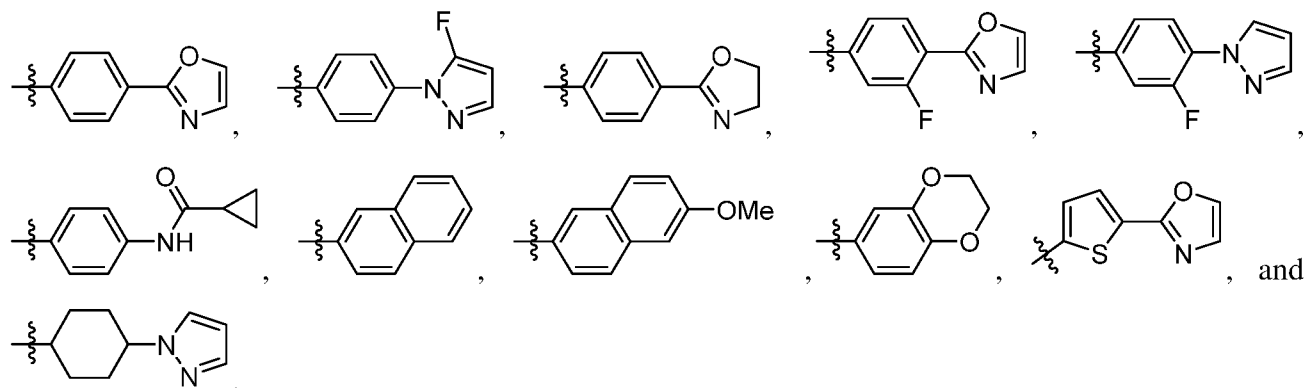
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^a.

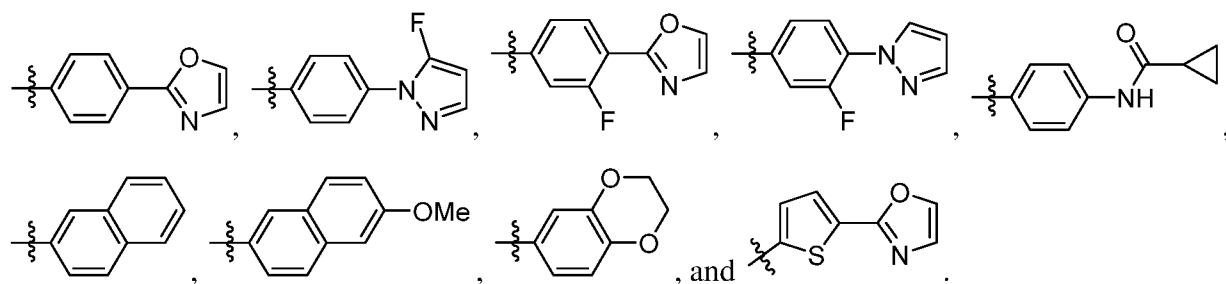
[0028] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is (i) monocyclic C₅-C₆carbocyclyl ring, (ii) phenyl ring, (iii) 5- to 6-membered monocyclic heteroaryl ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, or (iv) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 6-membered carbocyclic ring or 5- to 6-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, and wherein Ring A is optionally substituted with one or more R^a. In some embodiments, Ring A is (i) a phenyl ring, (ii) 5- to 6-membered monocyclic heteroaryl ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, or (iii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 6-membered carbocyclic ring or 5- to 6-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, and wherein Ring A is optionally substituted with one or more R^a. In some embodiments, Ring A is (i) a phenyl ring or (ii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 6-membered carbocyclic ring or 5- to 6-membered heterocyclic ring

containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, and wherein Ring A is optionally substituted with one or more R^a . In some embodiments, Ring A is phenyl or naphthyl optionally substituted with one or more R^a . In some embodiments, Ring A is phenyl optionally substituted with one or more R^a . In some embodiments, Ring A is a phenyl ring substituted with at least one R^a in the para position.

[0029] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is selected from:



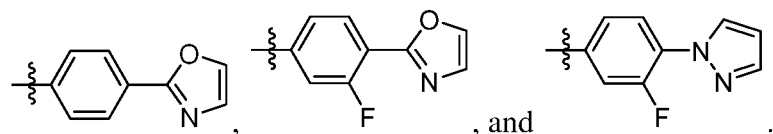
[0030] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is selected from:



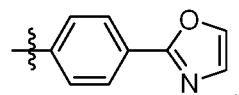
[0031] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is selected from:



[0032] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is selected from:



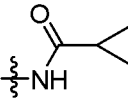
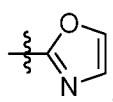
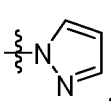
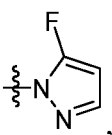
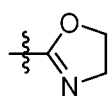
[0033] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and V, Ring A is:

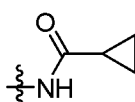
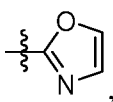
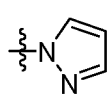
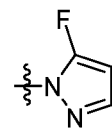


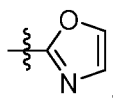
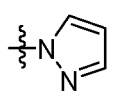
[0034] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R^a is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R',

-NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic. In some embodiments, each R^a is independently halogen, -OR, -NRC(O)R', optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, or optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen. In some embodiments, each R^a is independently halogen or optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen. In some embodiments, each R^a is independently halogen or optionally substituted 5-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen.

[0035] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and

VIII-b, each R^a is independently selected from the group consisting of fluoro, -OMe, , , , , and . In some embodiments, each R^a is independently selected

from the group consisting of fluoro, -OMe, , , , . In some

embodiments, each R^a is independently selected from the group consisting of fluoro, , and .

[0036] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring B is optionally substituted with one or more R^b.

[0037] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^b; or

(ii) a bicyclic 6- to 12-membered ring comprising a C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,

wherein the C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^b.

[0038] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl,

wherein the monocyclic ring is optionally substituted with one or more R^b; or

(ii) a bicyclic 9- to 12-membered ring comprising a phenyl ring,

wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

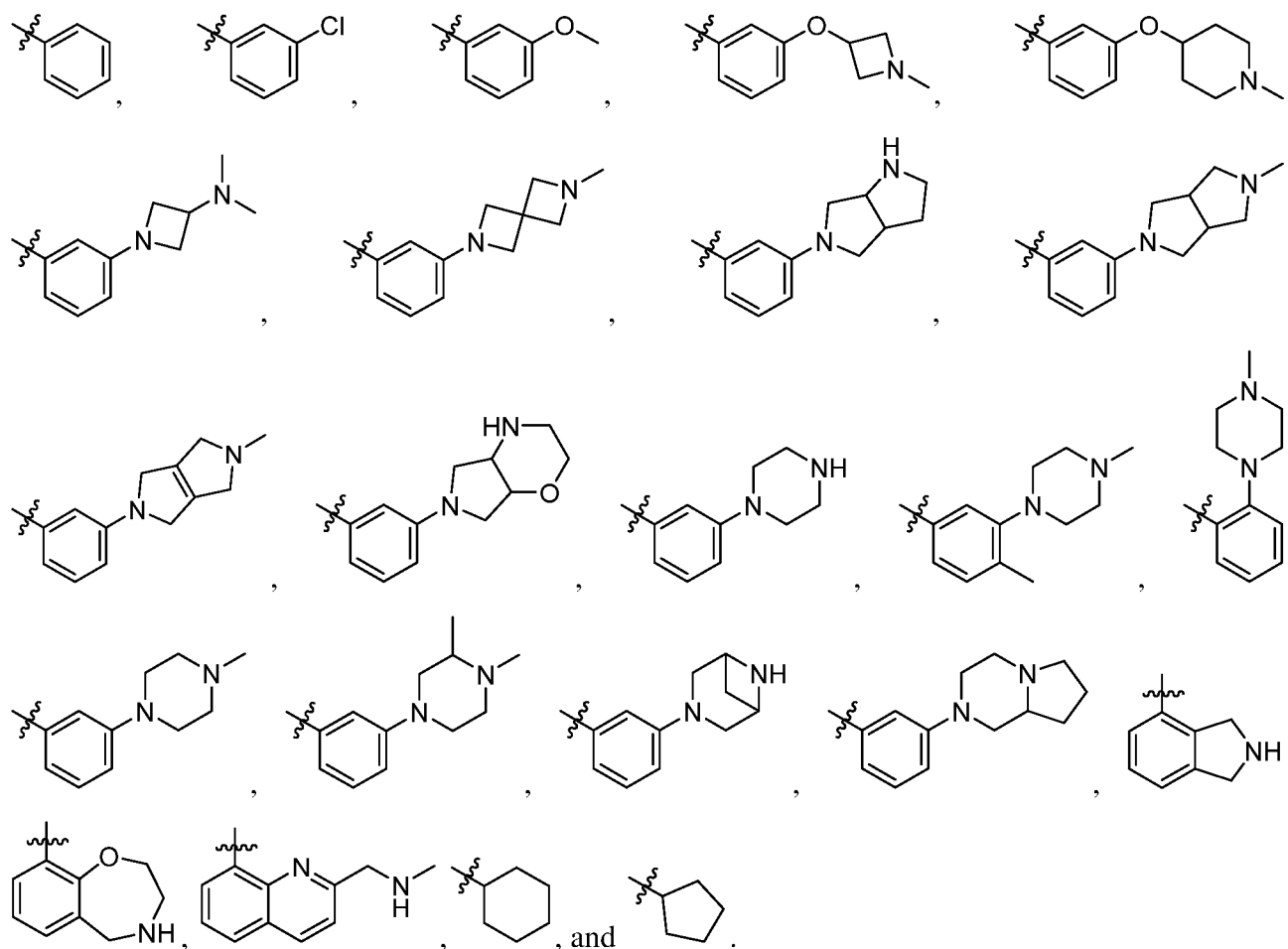
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^b.

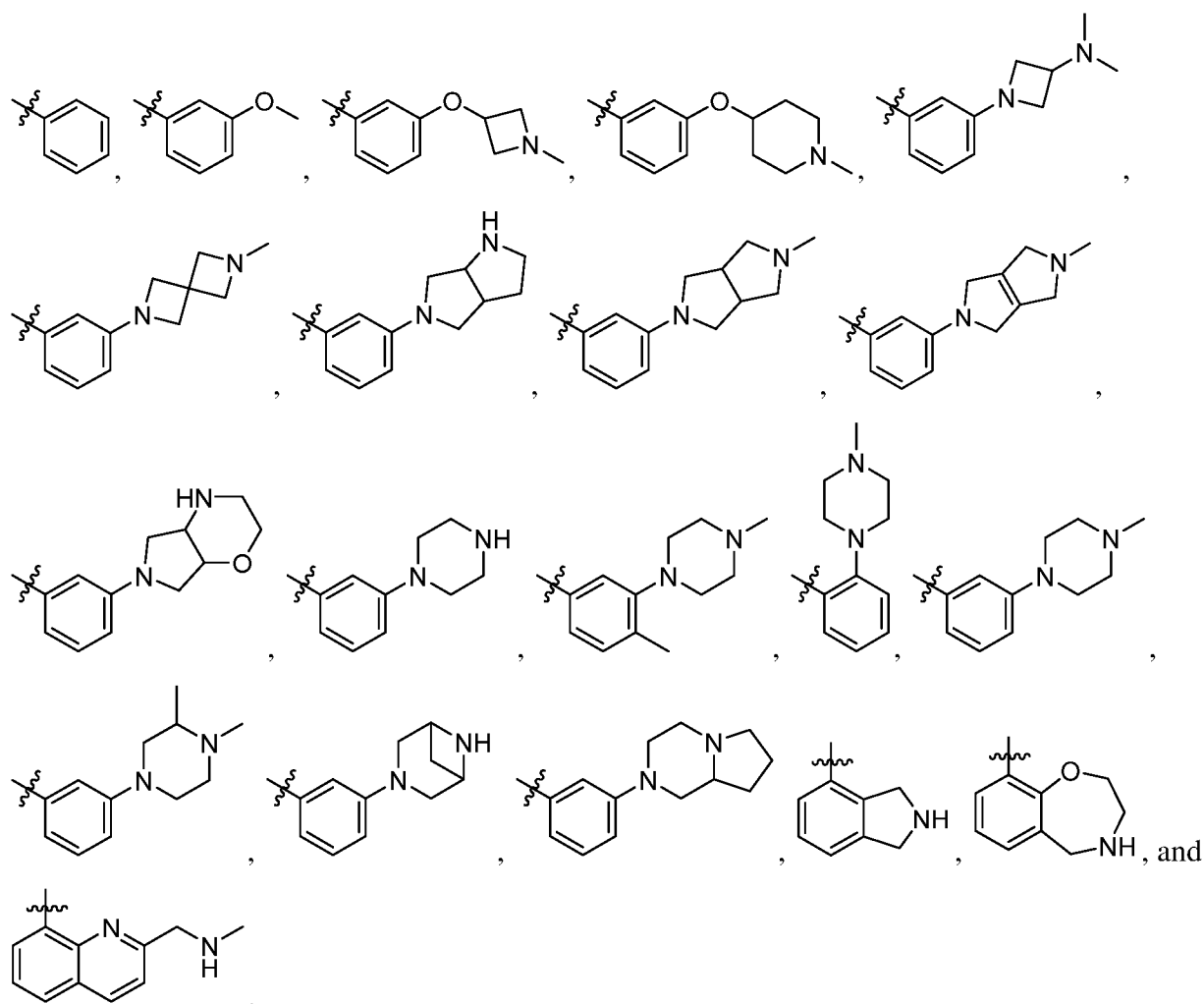
[0039] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is (i) monocyclic C₅-C₆carbocyclyl ring, (ii) phenyl ring, (iii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 7-membered carbocyclic ring or 5- to 7-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, and wherein Ring B is optionally substituted with

one or more R^b . In some embodiments, Ring B is (i) phenyl ring or (ii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 7-membered carbocyclic ring or 5- to 7-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, and wherein Ring B is optionally substituted with one or more R^b . In some embodiments, Ring B is a phenyl ring optionally substituted with one or more R^b . In some embodiments, Ring B is a phenyl ring substituted with at least one R^b in the meta position.

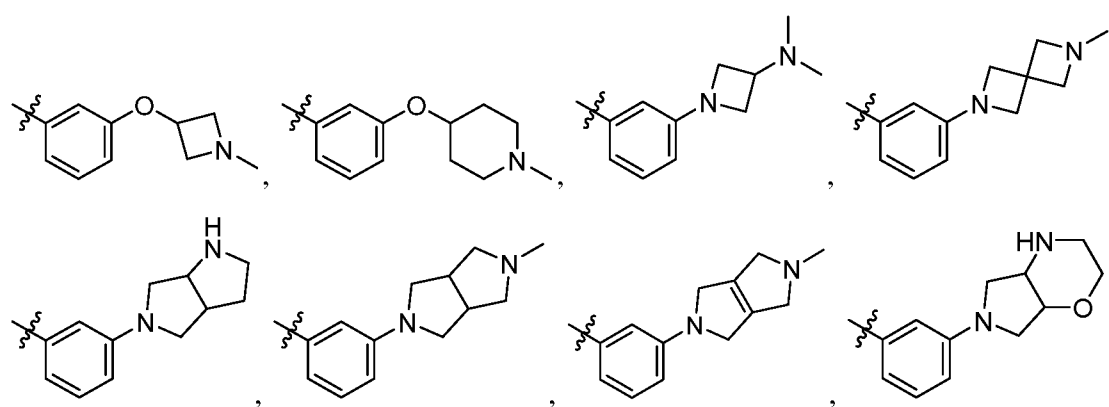
[0040] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is selected from:

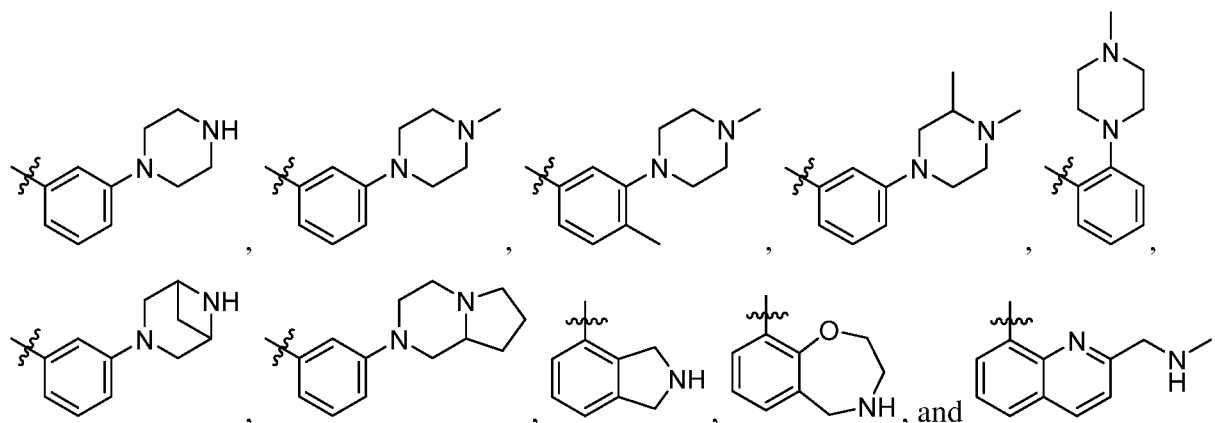


[0041] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is selected from:



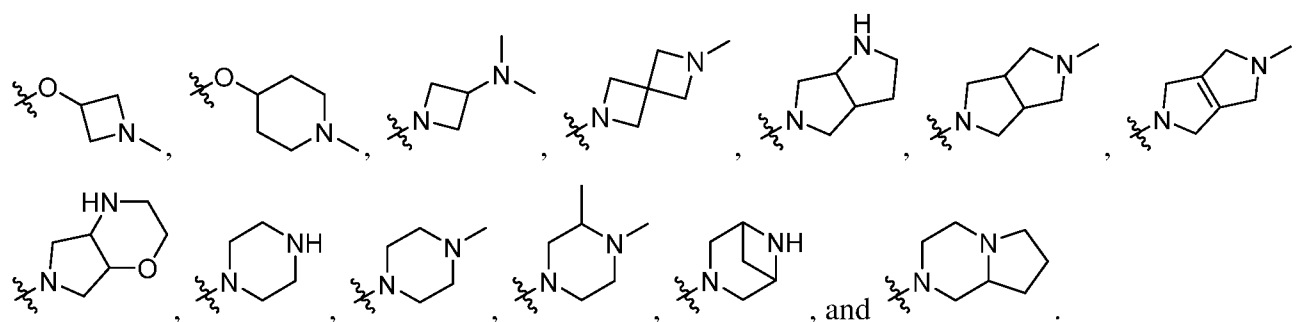
[0042] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, and VI, Ring B is selected from:



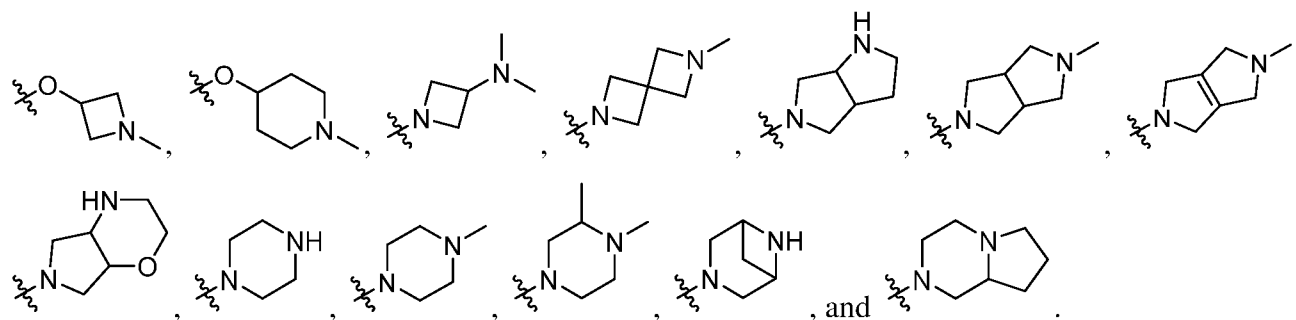


[0043] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R^b is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^b group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆ aliphatic. In some embodiments, each R^b is independently selected from the group consisting of halogen, -OR, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of -NR₂ and C₁-C₆ aliphatic. In some embodiments, each R^b is independently selected from the group consisting of -OR, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of -NR₂ and C₁-C₆ aliphatic.

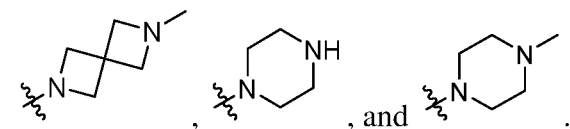
[0044] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R^b is independently selected from the group consisting of chloro, -OMe, methyl, -CH₂NHMe,



[0045] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R^b is independently selected from the group consisting of -OMe, methyl, $-CH_2NHMe$,



[0046] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R^b is independently selected from the group consisting of methyl,



[0047] In some embodiments of Formulas I, II, and III, R^1 and R^2 are each independently selected from the group consisting of:

-H, halogen, -OR, $-OC(O)R'$, $-OS(O)_2R'$, $-OS(O)_2NR_2$, $-OC(O)NR_2$, $-OC(O)OR$, $-NR_2$, $-NRC(O)R'$, $-NRS(O)_2R'$, $-NRC(O)NR_2$, $-NRC(O)OR$, -CN, $-NO_2$, -SR, $-C(O)R'$, $-C(O)OR$, $-C(O)NR_2$, $-S(O)_2R'$, $-SO_2NR_2$, $-S(O)_2OR$, optionally substituted C_1 - C_6 aliphatic, optionally substituted C_3 - C_{10} cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S,

or R^1 and R^2 combine with the carbon to which they are attached to form an optionally substituted C_3 - C_8 cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R^1 and R^2 group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic.

[0048] In some embodiments of Formulas I, II, and III, R^1 and R^2 are each independently selected from the group consisting of -H, -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic. In some embodiments, R^1 and R^2 are each independently selected from the group consisting of -H, -OR, -CN, and C₁-C₆aliphatic. In some embodiments, R^1 and R^2 are each independently selected from the group consisting of -H and -OR. In some embodiments, R^2 is -H.

[0049] In some embodiments of Formulas I, II, and III, R^1 and R^2 are each independently selected from the group consisting of -H, -OH, -OMe, -NH₂, -NHMe, -CN, -C(O)NHMe, and methyl. In some embodiments, R^1 and R^2 are each independently selected from the group consisting of -H, -OH, -OMe, -CN, and methyl. In some embodiments, R^1 and R^2 are each independently selected from the group consisting of -H, -OH, and -OMe. In some embodiments, R^2 is -H. In some embodiments, R^1 is -OH, and R^2 is -H.

[0050] In some embodiments of Formulas IV, IV-a, IV-b, V, VI, and VII, R^1 is selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclcyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^1 group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic.

[0051] In some embodiments of Formulas IV, IV-a, IV-b, V, VI, and VII, R^1 is selected from the group consisting of -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic. In some embodiments, R^1 is selected from the group consisting of -H, -OR, -CN, and C₁-C₆aliphatic. In some embodiments, R^1 is -OR. In some embodiments, R^1 is -OR, and m is 0.

[0052] In some embodiments of Formulas IV, IV-a, IV-b, V, VI, and VII, R^1 is selected from the group consisting of -OH, -OMe, -NH₂, -NHMe, -CN, -C(O)NHMe, and methyl. In some embodiments, R^1 is selected from the group consisting of -OH, -OMe, -CN, and methyl. In some embodiments, R^1

is selected from the group consisting of -OH and -OMe. In some embodiments, R¹ is -OH. In some embodiments, R¹ is -OH, and m is 0.

[0053] In some embodiments of Formulas I, II, and III, R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of:

-H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₈cycloalkyl, and optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

or R³ and R⁴, or R⁵ and R⁶, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R³, R⁴, R⁵, and R⁶ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆ aliphatic.

[0054] In some embodiments of Formulas I, II, and III, R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H and C₁-C₆aliphatic. In some embodiments, R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H and methyl. In some embodiments, R³, R⁴, R⁵, and R⁶ are each -H. In some embodiments, R³ is methyl, and R⁴, R⁵, and R⁶ are each -H. In some embodiments, R⁵ is methyl, and R³, R⁴, and R⁶ are each -H.

[0055] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, and optionally substituted C₁-C₆aliphatic, wherein an optionally substituted R⁷, R⁸, and R⁹ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic. In some embodiments, R⁷, R⁸, and R⁹, if present, are each independently selected from the group consisting of -H, halogen, -OR, -NR₂, -CN, and C₁-C₆aliphatic optionally substituted with halogen. In some embodiments, R⁷, R⁸, and R⁹, if present, are each independently selected from the group consisting of -H, -OR, and C₁-C₆aliphatic. In some embodiments, R⁷, R⁸, and R⁹, if present, are each independently selected from the group consisting of -H, -OMe, and methyl. In some embodiments, R⁷, R⁸, and R⁹, if present, are each -H. In some embodiments, R⁷ is selected from the

group consisting of -H, -OR, and C₁-C₆aliphatic. In some embodiments, R⁷ is selected from the group consisting of -H, -OMe, and methyl. In some embodiments, R⁷ is -H. In some embodiments, R⁸ is selected from the group consisting of -H, -OR, and C₁-C₆aliphatic. In some embodiments, R⁸ is selected from the group consisting of -H, -OMe, and methyl. In some embodiments, R⁸ is -H. In some embodiments, R⁹ is selected from the group consisting of -H, -OR, and C₁-C₆aliphatic. In some embodiments, R⁹ is selected from the group consisting of -H, -OMe, and methyl. In some embodiments, R⁹ is -H.

[0056] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R group may be optionally substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic. In some embodiments, each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R group may be optionally substituted with one or more C₁-C₆aliphatic. In some embodiments, each R is independently selected from the group consisting of -H, methyl, and 4- to 6-membered heterocyclyl containing 1-2 heteroatoms independently selected from N, O, and S optionally substituted with methyl. In some embodiments, each R is -H.

[0057] In some embodiments, of Formulas I, II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, each R' is independently selected from the group consisting of optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-3 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R' group may be substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic. In some embodiments, each R' is independently C₁-C₆aliphatic or C₃-C₁₀cycloalkyl. In some embodiments, each R' is independently C₃-C₁₀cycloalkyl. In some embodiments, each R' is cyclopropyl.

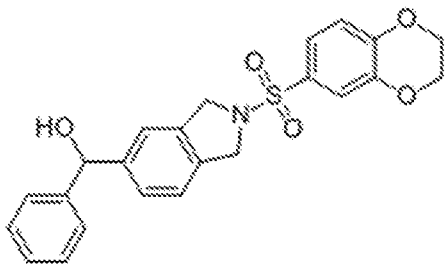
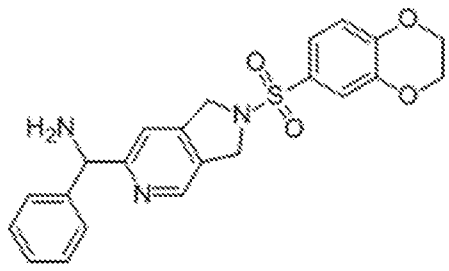
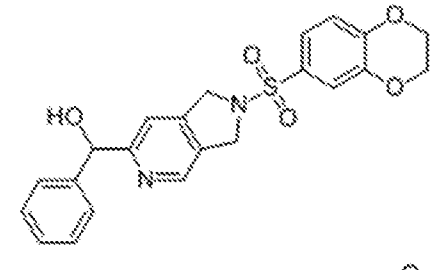
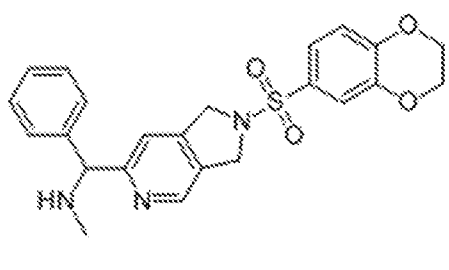
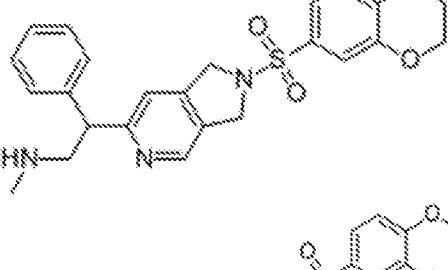
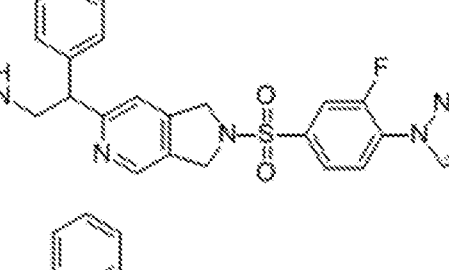
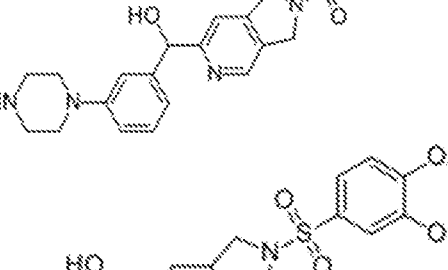
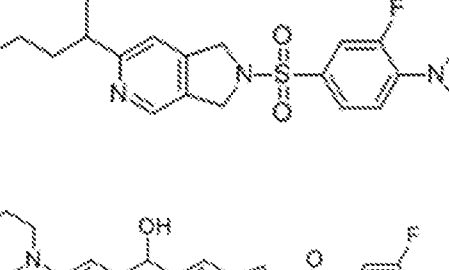
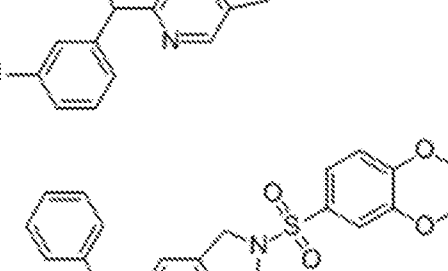
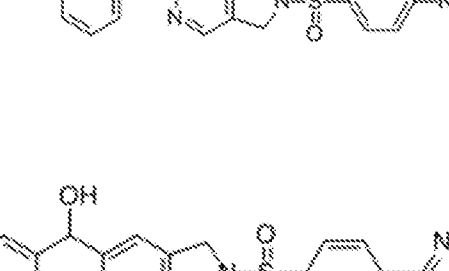
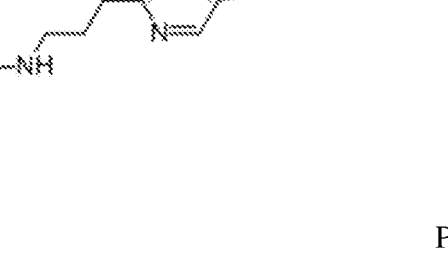
[0058] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, and VII, m is 0, 1, or 2. In some embodiments, m is 0. In some embodiments, m is 0 or 1. In some embodiments, m is 0 or 2. In some embodiments, m is 1 or 2.

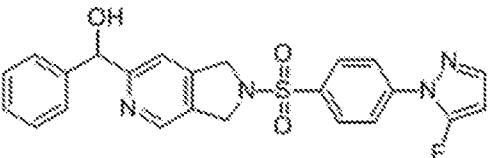
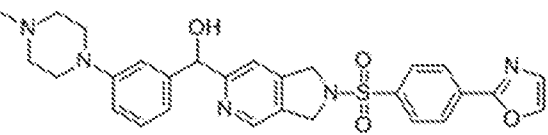
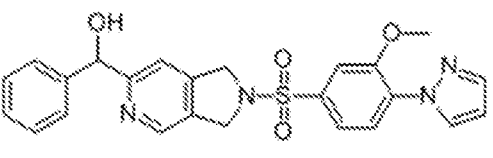
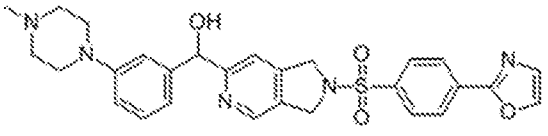
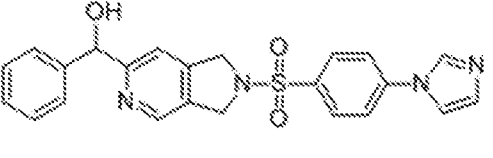
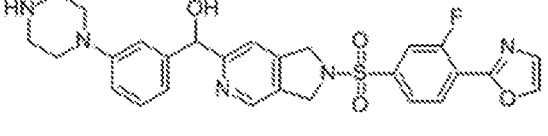
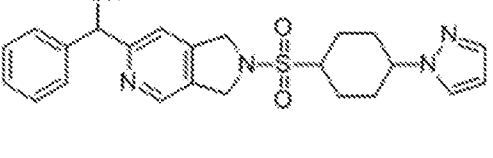
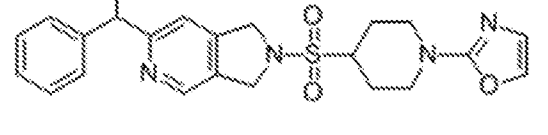
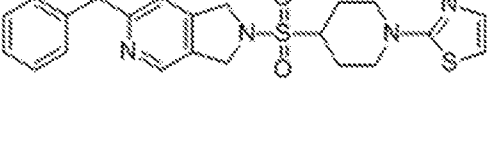
[0059] In some embodiments of Formulas I, II, III, IV, IV-a, IV-b, V, VI, and VII, n is 0, 1, or 2. In some embodiments, n is 0. In some embodiments, n is 0 or 1. In some embodiments, n is 0 or 2. In some embodiments, n is 1 or 2.

[0060] In some embodiments of Formulas IV, IV-a, IV-b, V, VI, and VII, m is 0, 1, or 2. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[0061] Another aspect of the present disclosure is a compound selected from Table 1, or a pharmaceutically acceptable salt thereof. It will be appreciated that in Table 1, where multiple Example numbers are indicated for a single chemical structure, each Example number refers to a stereoisomer of the compound. See Table 16 for additional information regarding such stereoisomers.

Table 1.

Ex.	Structure	Ex.	Structure
1 and 2		10	
3 and 4		11	
5 and 6		12	
7		13	
8		14 and 15	
9		16	

Ex.	Structure	Ex.	Structure
17		28	
18		29 and 30	
19		31	
20, 21, 22, and 23		32	
24		33	
25		34	
26 and 27		35	

Ex.	Structure	Ex.	Structure
36		46 and 47	
37		48 and 49	
38 and 39		50 and 51	
40 and 41		52 and 53	
42 and 43		54	
44		55 and 56	
45		57 and 58	

Ex.	Structure	Ex.	Structure
59 and 60		76 and 77	
61, 62, 63, and 64		78 and 79	
65, 66, 67, and 68		80 and 81	
69 and 70		82 and 83	
71 and 72		84 and 85	
73 and 74		86, 87, 88, and 89	
75		90 and 91	

Ex.	Structure	Ex.	Structure
92, 93, 94, and 95		104 and 105	
96 and 97		106 and 107	
98 and 99		108 and 109	
100 and 101		110	
102 and 103			

[0062] It will be appreciated that throughout the present disclosure, unless otherwise indicated, reference to a compound of Formula I is intended to also include II, III, IV, IV-a, IV-b, V, VI, VII, VIII, VIII-a, and VIII-b, and compound species of such formulas disclosed herein.

[0063] Unless otherwise stated, it will be appreciated that when “one or more” substituents are recited for a particular variable, it includes one, two, three, four, or more substituents as valency permits.

[0064] Unless otherwise stated, structures depicted herein are also meant to include all stereoisomeric (e.g., enantiomeric or diastereomeric) forms of the structure, as well as all geometric or conformational isomeric forms of the structure; for example, the R and S configurations for each stereocenter. Therefore, single stereochemical isomers, as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. For example, in some cases Table 1 shows one or more stereoisomers of a compound, and unless otherwise indicated, represents each stereoisomer alone and/or as a mixture. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure.

[0065] In some embodiments, a compound of Formula I is obtained by a process comprising a purification method in Table 15. In some embodiments, the compound is obtained by a process comprising a purification method in Table 15 and is the 1st eluting isomer of the purification method. In some embodiments, the compound is obtained by a process comprising a purification method in Table 15 and is the 2nd eluting isomer of the purification method. In some embodiments, the compound is obtained by a process comprising a purification method in Table 15 and is the 3rd eluting isomer of the purification method. In some embodiments, the compound is obtained by a process comprising a purification method in Table 15 and is the 4th eluting isomer of the purification method. In some embodiments, the compound is obtained by a process comprising a purification method in Table 15 and is the 5th, 6th, 7th, or 8th eluting isomer of the purification method.

[0066] In some embodiments, a USP9X Inhibitor is obtained by a process comprising a purification method in Table 15. In some embodiments, the USP9X Inhibitor is obtained by a process comprising a purification method in Table 15 and is the 1st eluting isomer of the purification method. In some embodiments, the USP9X Inhibitor is obtained by a process comprising a purification method in Table 15 and is the 2nd eluting isomer of the purification method. In some embodiments, the USP9X Inhibitor is obtained by a process comprising a purification method in Table 15 and is the 3rd eluting isomer of the purification method. In some embodiments, the USP9X Inhibitor is obtained by a process comprising a purification method in Table 15 and is the 4th eluting isomer of the purification method.

In some embodiments, the USP9X Inhibitor is obtained by a process comprising a purification method in Table 15 and is the 5th, 6th, 7th, or 8th eluting isomer of the purification method.

[0067] Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure.

[0068] The disclosure also provides compounds of Formula I (e.g., compounds that are not USP9X Inhibitors) that are useful, for example, as analytical tools and/or control compounds in biological assays.

[0069] The compounds of Formula I may form salts which are also within the scope of this disclosure. Reference to a compound of the Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. 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, 66: 1-19 (1977).

[0070] The disclosure also includes pharmaceutical compositions comprising one or more compounds as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some embodiments, pharmaceutical compositions reported herein can be provided in a unit dosage form (e.g., capsule, tablet or the like). In some embodiments, pharmaceutical compositions reported herein can be provided in an oral dosage form. In some embodiments, the pharmaceutical composition is orally administered in any orally acceptable dosage form. In some embodiments, an oral dosage form of a compound of Formula I can be a capsule. In some embodiments, an oral dosage form of a compound of Formula I is a tablet. In some embodiments, an oral dosage form comprises one or more fillers, disintegrants, lubricants, glidants, anti-adherents, and/or anti-statics. In some embodiments, an oral dosage form is prepared via dry blending. In some embodiments, an oral dosage form is a tablet and is prepared via dry granulation.

Methods of Using the Disclosed Compounds

[0071] Another aspect of the present disclosure is the use of compounds of Formula I. Compounds of Formula I are useful in medicine. For example, compounds and compositions described herein are inhibitors of USP9X. Methods of treatment (e.g., by inhibiting USP9X) can comprise administering to a subject in need thereof a therapeutically effective amount of (i) a compound disclosed herein, or

a pharmaceutically acceptable salt thereof, or (ii) a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In some embodiments, a method of treating a disease associated with modulation of USP9X comprises administering a therapeutically effective amount of a compound disclosed herein. In some embodiments, a method of treating cancer comprises administering a therapeutically effective amount of a compound disclosed herein.

Methods of Synthesizing the Disclosed Compounds

[0072] The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

Examples

Analytical Methods, Materials, and Instrumentation

[0073] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Unless otherwise noted, reactions were conducted under an inert atmosphere of nitrogen. NMR instrument: Bruker BBFO ASCEND™400 AVANCE III 400 MHz and Bruker BBFO ULTRASHIELD™300 AVANCE III 300 MHz. Internal standard: Tetramethylsilane (TMS). MassSpec instruments and ionization method: Shimadzu LC-2020, electrospray ionization, ESI. Chromatography instruments (Reverse phase chromatography: Agela TechnologiesMP200. Preparatory HPLC (Prep-HPLC): Waters. Supercritical fluid chromatography (SFC): Shimadzu).

Abbreviations

Ac ₂ O	Acetic anhydride
ACN	Acetonitrile
AcOH	Acetic acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
atm	atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BTMG	2- <i>tert</i> -Butyl-1,1,3,3-tetramethylguanidine
CbzCl	Benzyl chloroformate
CDI	1,1'-Carbonyldiimidazole
Cp*Ru(cod)Cl	Chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(II)

δ	chemical shift
DCM	Dichloromethane or methylene chloride
DCE	1,2-Dichloroethane
DEA	Diethylamine
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DME	Dimethoxyethane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EA	Ethyl acetate
EDCI	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EDTA	Ethylenediaminetetraacetic acid
ee	enantiomeric excess
h	hour
^1H NMR	proton nuclear magnetic resonance
HATU	2-(3H-[1,2,3]Triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate
HOBT	1H-Benzo[d][1,2,3]triazol-1-ol hydrate
HPLC	high performance liquid chromatography
Hz	Hertz
IPA	Isopropyl alcohol
LAH	lithium aluminum hydride
LCMS	liquid chromatography/mass spectrometry
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	m-Chloroperoxybenzoic acid
MeOH	Methanol
min	minutes
MS	mass spectrometry

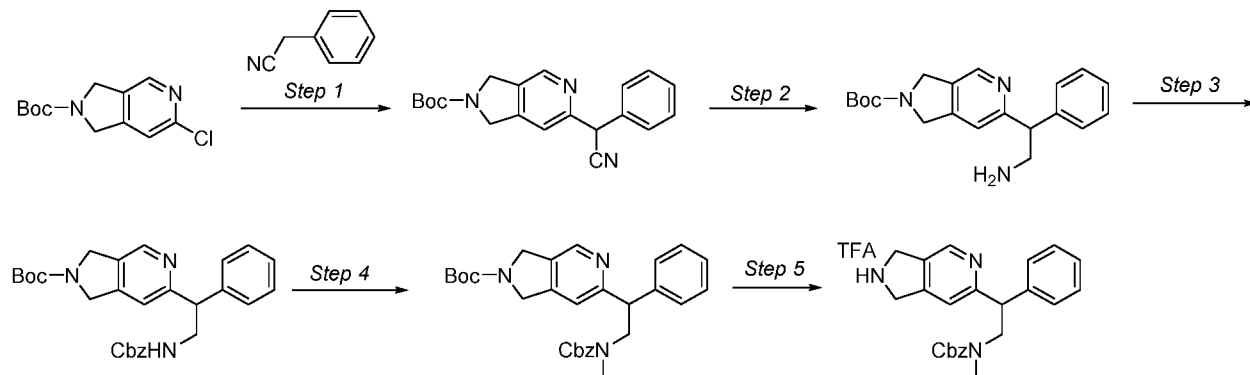
NMM	4-Methylmorpholine
NMP	N-Methyl-2-pyrrolidone
$\text{Pd}_2(\text{dba})_3 \cdot \text{CH}_2\text{Cl}_2$	Tris(dibenzylideneacetone)dipalladium(0) chloroform adduct
$\text{Pd}(\text{dppf})\text{Cl}_2$	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$\text{Pd}(\text{PPh}_3)_4$	Tetrakis(triphenylphosphine)palladium (0)
PE	Petroleum ether
PTSA	4-methylbenzenesulfonic acid
rt	room temperature
Rt	retention time
$\text{RuCl}_2[(R)\text{-DM-BINAP}]$ [(R)-DAIPEN]	Dichloro[(S)-(-)-2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl][(2S)-(+)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine]ruthenium(II)
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
RuPhos 2G	Chloro(2-dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
TBDMS-Cl	tert-butyl dimethylsilyl chloride
tBuXPhos 3G	[(2-Di- <i>tert</i> -butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos 2G	Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)
XPhos 3G	Methanesulfonato(2-dicyclohexylphosphino-2',4',6'-tri- <i>i</i> -propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl)palladium(II) dichloromethane adduct
SelectFluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
STAB	Sodium triacetoxymethylborohydride

PFA

Paraformaldehyde

Example 1. Synthesis of Intermediates

Intermediate 1-1. [(2S)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl] (methyl)amine; [(2R)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl](methyl) amine

**Step 1. Tert-butyl 6-[cyano(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate**

[0074] To a solution of tert-butyl 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (300 mg, 1.18 mmol) in THF (3 mL) was added 2-phenylacetonitrile (152 mg, 1.30 mmol) and sodium amide (92 mg, 2.36 mmol). The resulting mixture was stirred for 30 min at 50 °C and then cooled to room temperature. The reaction mixture was poured into brine (5 mL) and then extracted with EA (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:3 EA/PE) to afford tert-butyl 6-[cyano(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (100 mg, 25%). LCMS (ES, m/z) 336 $[M+H]^+$.

Step 2. Tert-butyl 6-(2-amino-1-phenylethyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0075] To a solution of tert-butyl 6-[cyano(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (100 mg, 0.30 mmol) in methanol (2 mL) was added Raney Ni (10 mg, 0.12 mmol). Then hydrogen was introduced with hydrogen balloon. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was filtered through a short pad of Celite and concentrated under vacuum to afford tert-butyl 6-(2-amino-1-phenylethyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (90 mg, 89%). LCMS (ES, m/z) 340 $[M+H]^+$.

Step 3. Tert-butyl 6-(2-[[[(benzyloxy)carbonyl]amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0076] To a solution of tert-butyl 6-(2-amino-1-phenylethyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (90 mg, 0.27 mmol) in DCM (1 mL) was added CbzCl (68 mg, 0.39 mmol) and TEA (54 mg, 0.53 mmol). The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was poured into brine (3 mL) and then extracted with EA (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 EA/PE) to afford tert-butyl 6-(2-[[[(benzyloxy)carbonyl]amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (110 mg, 88%). LCMS (ES, m/z) 474 $[M+H]^+$.

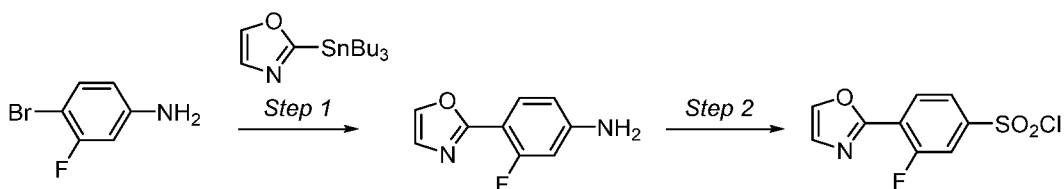
Step 4. Tert-butyl 6-(2-[[[(benzyloxy)carbonyl](methyl)amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0077] To a solution of tert-butyl 6-(2-[[[(benzyloxy)carbonyl]amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (110 mg, 0.23 mmol) in THF (1 mL) was added sodium hydride (11 mg, 0.28 mmol, 60% dispersion in mineral oil) with stirring at 0 °C. After stirring for 30 min at 0 °C, iodomethane (66 mg, 0.46 mmol) was added in dropwise. The resulting mixture was stirred for 2 h at rt and then poured into brine (3 mL) and then extracted with EA (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 EA/PE) to afford tert-butyl 6-(2-[[[(benzyloxy)carbonyl](methyl)amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (100 mg, 88%). LCMS (ES, m/z) 488 $[M+H]^+$.

Step 5. Benzyl N-methyl-N-(2-phenyl-2-[1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]ethyl)carbamate (TFA salt)

[0078] To a solution of tert-butyl 6-(2-[[[(benzyloxy)carbonyl](methyl)amino]-1-phenylethyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (100 mg, 0.21 mmol) in dichloromethane (1 mL) was added TFA (0.2 mL). The resulting solution was stirred for 1 h at room temperature and concentrated under vacuum to afford benzyl N-methyl-N-(2-phenyl-2-[1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]ethyl)carbamate (TFA salt) as light brown oil (100 mg, crude). LCMS (ES, m/z) 388 $[M+H]^+$.

Intermediate 2-1. (3-bromophenyl)([2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol



Step 1. 3-fluoro-4-(1,3-oxazol-2-yl)aniline

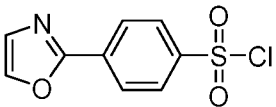
[0079] To a solution of 4-bromo-3-fluoroaniline (474 mg, 2.51 mmol) in 1,4-dioxane (10 mL) was added Pd(dppf)Cl₂ (183 mg, 0.25 mmol) and 2-(tributylstannyl)-1,3-oxazole (900 mg, 2.52 mmol). The resulting mixture was stirred for 48 h at 100 °C and then cooled to room temperature. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 3-fluoro-4-(1,3-oxazol-2-yl)aniline (180 mg, 41%). LCMS (ES, *m/z*) 179 [M+H]⁺.

Step 2. 3-fluoro-4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride

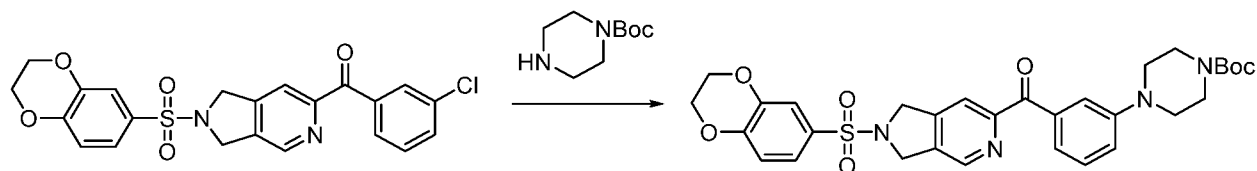
[0080] Into glacial acetic acid (10 mL) was bubbled in SO₂ gas for 1 h at room temperature. Then CuCl₂ (34 mg, 0.25 mmol) was added and SO₂ gas was bubbled in for additional 2 h to afford solution A. To a pre-cooled solution of 3-fluoro-4-(1,3-oxazol-2-yl)aniline (180 mg, 1.01 mmol) in acetic acid (2 mL) and concentrated hydrochloric acid (6 mL) was added a solution of sodium nitrite (77 mg, 1.11 mmol) in distilled water (0.5 mL) dropwise with stirring at -10 °C. After stirring for 15 min, solution A was added to this diazonium salt solution at -10 °C. The resulting solution was allowed to warm to room temperature naturally and stirred for 16 h. The reaction mixture was treated with water (10 mL) and then extracted with EA (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 12:88 ethyl acetate/petroleum ether) to afford 3-fluoro-4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride (120 mg, 45%). LCMS (ES, *m/z*) 262, 264 [M+H]⁺.

[0081] The Intermediates in Table 2 were synthesized according to the procedure described for Intermediate 2-1 above.

Table 2.

Intermediate	Compound	LCMS: (ESI) <i>m/z</i> [M+H] ⁺
2-2	 4-(oxazol-2-yl)benzenesulfonyl chloride	244

Intermediate 3-1. 1-tert-butyl-6-(3-[[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]carbonyl]phenyl)-1λ³,3,6-oxadiazocan-2-one

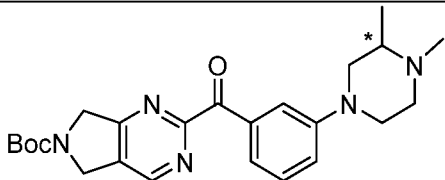
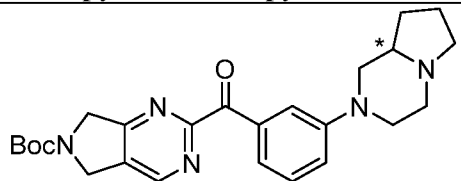
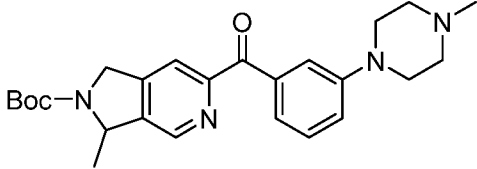
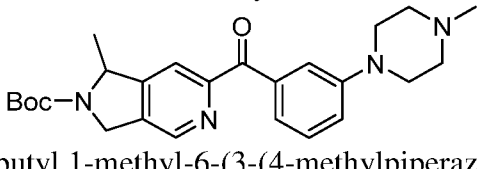
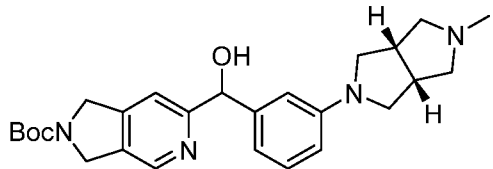
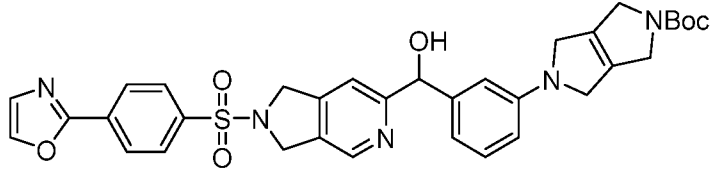


[0082] To a solution of 6-[(3-chlorophenyl)carbonyl]-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine (80 mg, 0.16 mmol) in toluene (8 mL) was added 1-tert-butyl-1λ3,3,6-oxadiazocan-2-one (42 mg, 0.22 mmol), XPhos (19 mg, 0.04 mmol), Cs₂CO₃ (171 mg, 0.52 mmol) and Pd₂(dba)₃·CHCl₃ (18 mg, 0.02 mmol). The resulting mixture was stirred for 16 h at 100 °C and then cooled to room temperature. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:10 EA/PE) to afford 1-tert-butyl-6-(3-[[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]carbonyl]phenyl)-1λ3,3,6-oxadiazocan-2-one as a yellow solid (80 mg, 84%). LCMS (ES, *m/z*) 607 [M+H]⁺.

[0083] The Intermediates in Table 3 were synthesized according to the procedure described for Intermediate 3-1 above.

Table 3.

Intermediate	Compound	LCMS: (ESI) <i>m/z</i> [M+H] ⁺
3-2	tert-butyl 2-(3-(4-methylpiperazin-1-yl)benzoyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	424
3-3	tert-butyl 4-(3-(hydroxy(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methyl)phenyl)piperazine-1-carboxylate	618
3-4 ^a	tert-butyl 6-(2-(4-methylpiperazin-1-yl)benzoyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	423

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
3-5 ^b	 tert-butyl 2-(3-(3,4-dimethylpiperazin-1-yl)benzoyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	438
3-6 ^c	 tert-butyl (S)-2-(3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)benzoyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	450
3-7 ^b	 tert-butyl 3-methyl-6-(3-(4-methylpiperazin-1-yl)benzoyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate  tert-butyl 1-methyl-6-(3-(4-methylpiperazin-1-yl)benzoyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	437
3-8 ^d	 tert-butyl 6-(hydroxy(3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenyl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	451
3-9 ^d	 tert-butyl 5-(3-(hydroxy(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-1-yl)methyl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-2-carboxylate	642

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
	c]pyridin-6-yl)methyl)phenyl)-3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate	

^aPd₂(dba)₃, BINAP, Cs₂CO₃, toluene, 100 °C, 16 h;

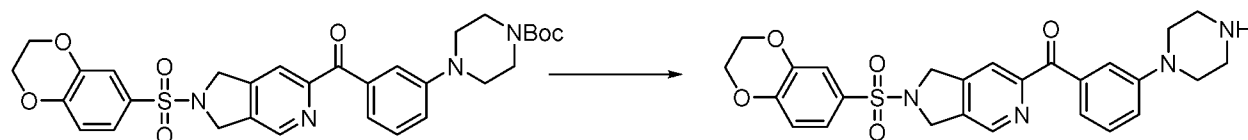
^bRuphos 3G, Ruphos, K₃PO₄, dioxane, 100 °C, 16 h;

^ctBuXPhos 3G, BTMG, THF, 60 °C;

^dRuphos 3G, Ruphos, Cs₂CO₃, dioxane, 100 °C, 16 h;

*Absolute stereochemistry not determined.

Intermediate 4-1. 1-(3-[[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]carbonyl]phenyl) piperazine

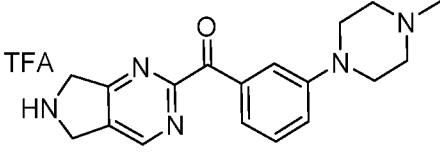
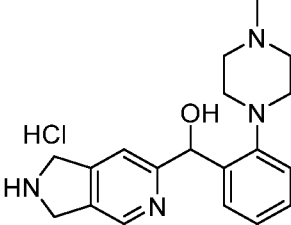
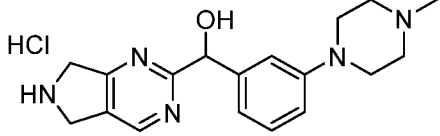
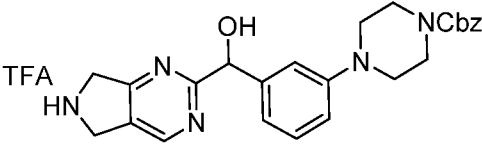
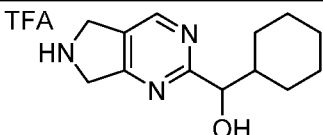
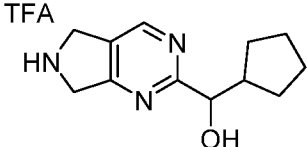


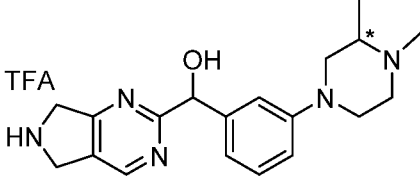
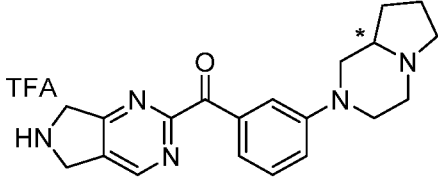
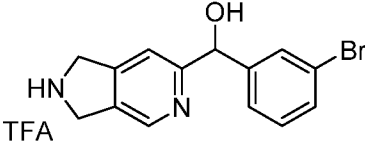
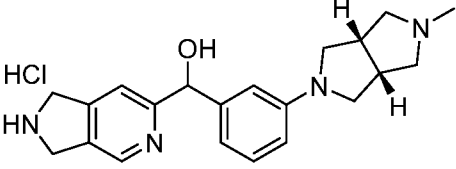
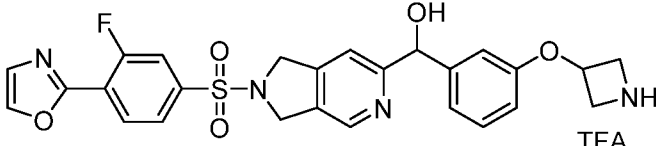
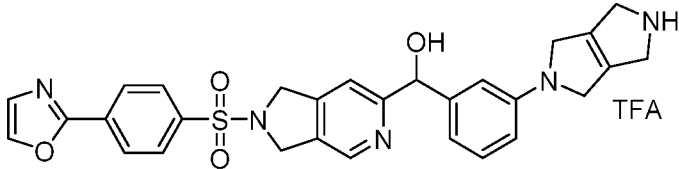
[0084] To a solution of tert-butyl 4-(3-(2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carbonyl)phenyl)piperazine-1-carboxylate (80 mg, 0.12 mmol) in DCM (3 mL) was added TFA (1 mL). The resulting solution was stirred for 1 h at rt and then concentrated under vacuum. The resulting mixture was then basified to pH 8 with saturated aqueous potassium carbonate solution. The resulting mixture was extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 1-(3-[[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]carbonyl]phenyl)piperazine as a yellow solid (50 mg, 83%). LCMS (ES, m/z) 507 [M+H]⁺.

[0085] The Intermediates in Table 4 were synthesized according to the procedure described for Intermediate 4-1 above.

Table 4.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
4-2	phenyl(2-(piperidin-4-ylsulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol- TFA salt	374

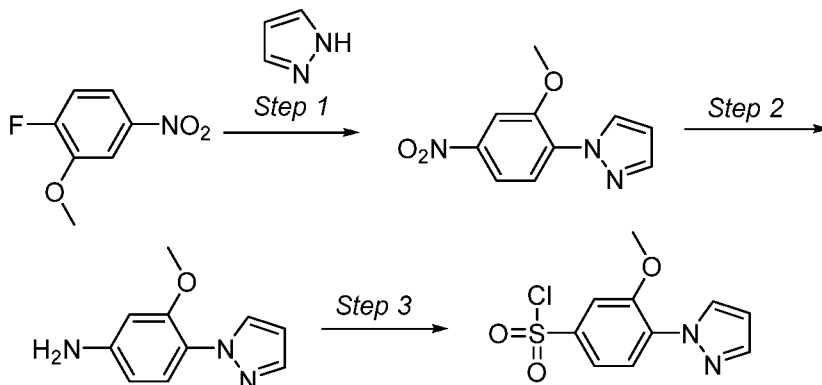
Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
4-3	 (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-(4-methylpiperazin-1-yl)phenyl)methanone TFA salt	324
4-4 ^a	 (2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(2-(4-methylpiperazin-1-yl)phenyl)methanol hydrochloride HCl salt	325
4-5 ^a	 (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-(4-methylpiperazin-1-yl)phenyl)methanol HCl salt	326
4-6	 benzyl 4-(3-((6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(hydroxymethyl)phenyl)piperazine-1-carboxylate TFA salt	446
4-7	 cyclohexyl(6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)methanol TFA salt	234
4-9	 cyclopentyl(6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)methanol TFA salt	220

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
4-11	 (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-(3,4-dimethylpiperazin-1-yl)phenyl)methanol TFA salt	340
4-12	 (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)methanone TFA salt	350
4-13	 (3-bromophenyl)(2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol TFA salt	305, 307
4-14 ^a	 (2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(3-((3aR,6aS)-5-methylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenyl)methanol HCl salt	351
4-15	 (3-(azetidin-3-yloxy)phenyl)(2-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol TFA salt	522
4-16	 (2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(3-(3,4,5,6-tetrahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenyl)methanol TFA salt	542

^aHCl salts were prepared from 4M HCl in dioxane in a stirred flask at room temperature;

*Absolute stereochemistry not determined.

Intermediate 5-1. Methyl 3-methoxy-4-(1H-pyrazol-1-yl)benzene-1-sulfonyl chloride



Step 1. 1-(2-Methoxy-4-nitrophenyl)-1H-pyrazole

[0086] To a solution of 1H-pyrazole (2 g, 29.4 mmol) in DMF (30 mL) was added 1-fluoro-2-methoxy-4-nitrobenzene (5 g, 29.2 mmol), and potassium carbonate (12 g, 86.8 mmol). The resulting mixture was stirred for 14 h at 120 °C and then cooled to room temperature. The reaction mixture was poured into water (30 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford 1-(2-methoxy-4-nitrophenyl)-1H-pyrazole as light yellow solid (5.0 g, 78%). LCMS (ES, *m/z*) 220 [M+H]⁺.

Step 2. 3-Methoxy-4-(1H-pyrazol-1-yl)aniline

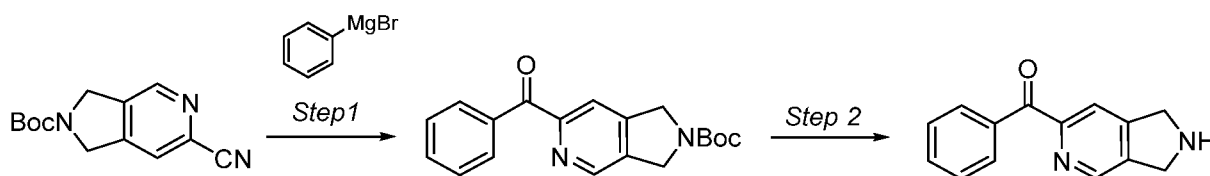
[0087] To a solution of 1-(2-methoxy-4-nitrophenyl)-1H-pyrazole (5 g, 22.8 mmol) in THF (30 mL) was added water (10 mL), EtOH (30 mL), iron powder (3.8 g, 68.1 mmol) and ammonium chloride (3.6 g, 67.3 mmol). The resulting mixture was stirred for 16 h at 80 °C and cooled to room temperature. The reaction mixture was filtered and extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 3-methoxy-4-(1H-pyrazol-1-yl) aniline as a black solid (4.9 g, crude). LCMS (ES, *m/z*) 190 [M+H]⁺.

Step 3. Methyl 3-methoxy-4-(1H-pyrazol-1-yl)benzene-1-sulfonyl chloride

[0088] Into glacial acetic acid (20 mL) was bubbled in SO₂ gas for 1 h at room temperature. Then CuCl₂ (800 mg, 5.95 mmol) was added and SO₂ gas was bubbled in for additional 2 h to afford solution A. To a pre-cooled solution of 3-methoxy-4-(1H-pyrazol-1-yl)aniline (4.5 g, 23.8 mmol) in acetic acid

(4 mL) and concentrated hydrochloric acid (12 mL) was added a solution of sodium nitrite (1.8 g, 26.1 mmol) in distilled water (5 mL) dropwise with stirring at -10 °C. After stirring for 15 min, solution A was added to this diazonium salt solution at -10 °C. The resulting solution was allowed to warm to room temperature naturally and stirred for 16 h. The reaction mixture was treated with water (100 mL) and then extracted with EA (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford methyl 3-methoxy-4-(1H-pyrazol-1-yl)benzene-1-sulfonyl chloride as a yellow solid (3.0 g, 46%). LCMS (EI, m/z): 273, 275 $[M+H]^+$.

Intermediate 6-1. 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine

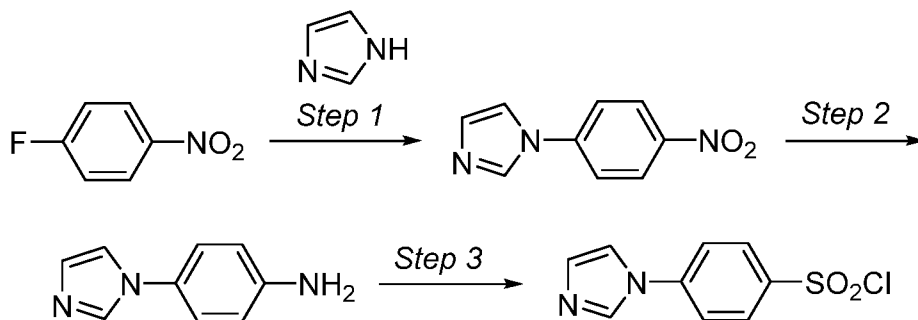


Step 1. Tert-butyl 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0089] To a solution of tert-butyl 6-cyano-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (670 mg, 2.73 mmol) in THF (10 mL), was added a solution of bromo(phenyl)magnesium (5.5 mL, 1 M in THF) at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction mixture was treated with 1 N HCl (10 mL) for 30 min and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford tert-butyl 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a white solid (600 mg, 68%). LCMS (ES, m/z) 325 $[M+H]^+$.

Step 2. 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine

[0090] To a solution of tert-butyl 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (200 mg, 0.62 mmol) in dichloromethane (4 mL) was added TFA (1 mL). The resulting solution was stirred for 2 h at room temperature and concentrated under vacuum. The resulting mixture was basified to pH 8 with saturated potassium carbonate solution and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine as brown oil (150 mg, crude). LCMS (ES, m/z) 225 $[M+H]^+$.

Intermediate 7-1. 4-(1H-imidazol-1-yl) benzene-1-sulfonyl chloride**Step 1. 1-(4-nitrophenyl)-1H-imidazole**

[0091] To a solution of 1-fluoro-4-nitrobenzene (3 g, 21.3 mmol), in N,N-dimethylformamide (30 mL), was added potassium carbonate (8.8 g, 63.7 mmol) and 1H-imidazole (1.4 g, 20.6 mmol). The resulting mixture was stirred for 18 h at 120 °C. The reaction mixture was cooled and poured into water (30 mL). The resulting solution was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:80 ethyl acetate/petroleum ether) to afford 1-(4-nitrophenyl)-1H-imidazole as a yellow solid (4.0 g, 99%). LCMS (ES, m/z) 190 $[M+H]^+$.

Step 2. 4-(1H-imidazol-1-yl)aniline

[0092] To a solution of 1-(4-nitrophenyl)-1H-imidazole (4 g, 21.14 mmol) in THF (30 mL), was added water (10 mL), EtOH (30 mL), iron powder (3.5 g, 62.7 mmol), and ammonium chloride (3.4 g, 63.6 mmol). The resulting mixture was stirred for 2 h at 80 °C and cooled to room temperature. The reaction mixture was filtered and extracted with EA (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 4-(1H-imidazol-1-yl) aniline as a black solid (2.0 g, 59%). LCMS (ES, m/z) 160 $[M+H]^+$.

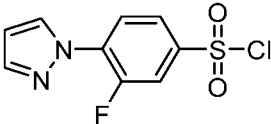
Step 3. 4-(1H-imidazol-1-yl) benzene-1-sulfonyl chloride

[0093] Into glacial acetic acid (20 mL) was bubbled SO₂ gas for 1 h at room temperature. Then CuCl₂ (210 mg, 1.56 mmol) was added and SO₂ gas was bubbled in for additional 2 h to afford solution A. To a pre-cooled solution of 4-(1H-imidazol-1-yl) aniline (1 g, 6.28 mmol) in acetic acid (4 mL) and concentrated hydrochloric acid (12 mL), was added a solution of sodium nitrite (470 mg, 6.09 mmol) in distilled water (1 mL) dropwise with stirring at -10 °C. After stirring for 15 min, solution A was added to this diazonium salt solution at -10 °C. The resulting solution was allowed to warm to

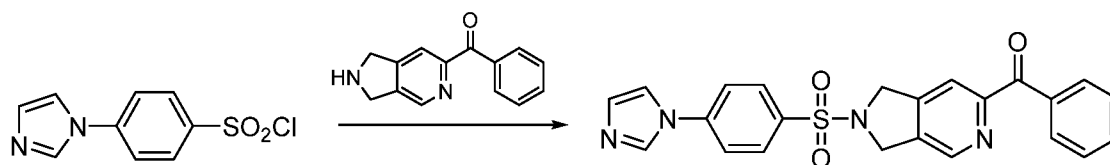
room temperature naturally and stirred for 16 h. The reaction mixture was treated with water (20 mL) and then extracted with EA (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 4-(1H-imidazol-1-yl) benzene-1-sulfonyl chloride as a white solid (400 mg, 26%). LCMS (EI, m/z): 243, 245 $[M+H]^+$.

[0094] The Intermediates in Table 5 were synthesized according to the procedure described for Intermediate 7-1 above.

Table 5.

Intermediate	Compound	LCMS: (ESI) m/z $[M+H]^+$
7-2	 3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl chloride	--

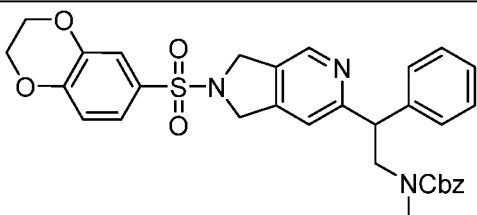
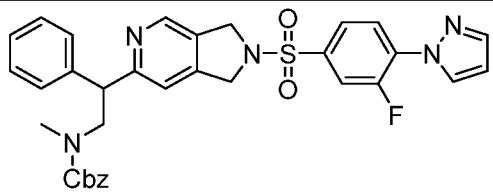
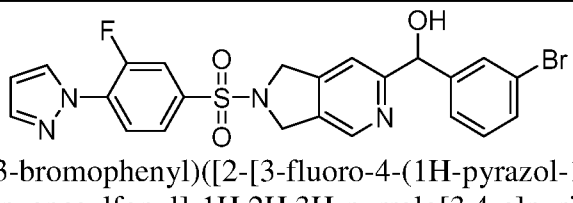
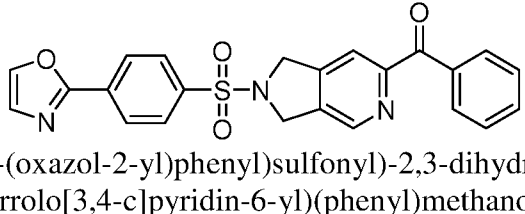
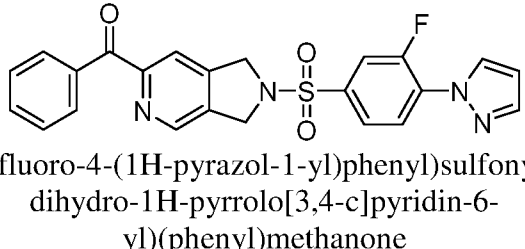
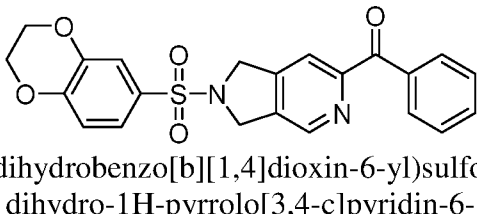
Intermediate 8-1. 1-[4-({6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridinyl)sulfonyl}phenyl]-1H-imidazole

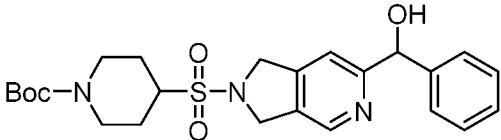
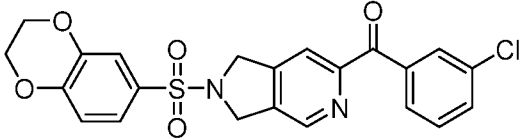
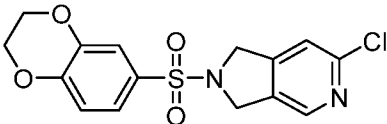
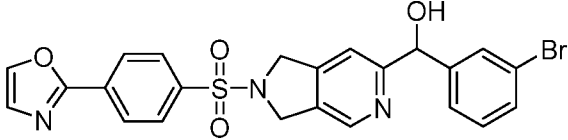
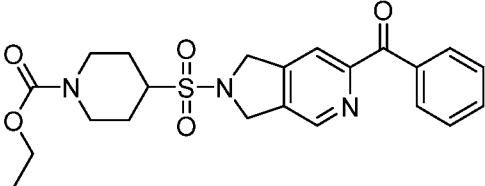
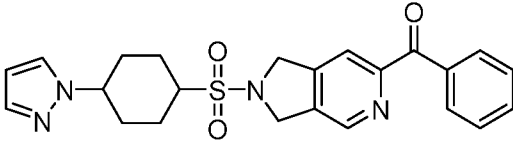
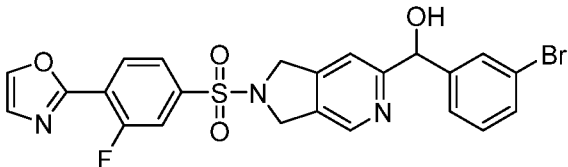


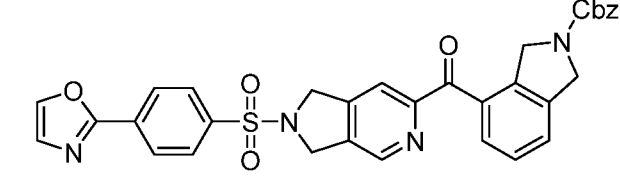
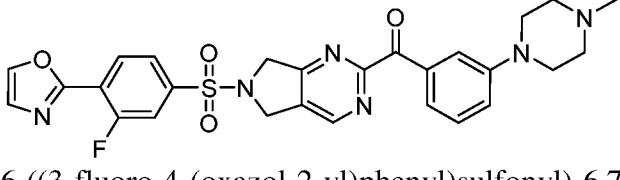
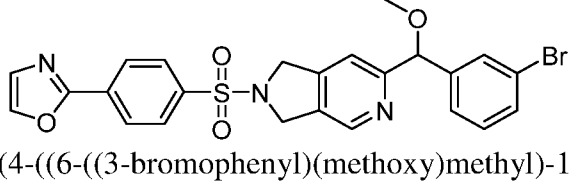
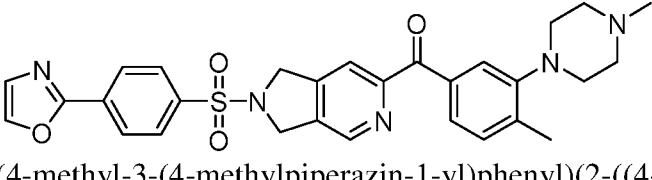
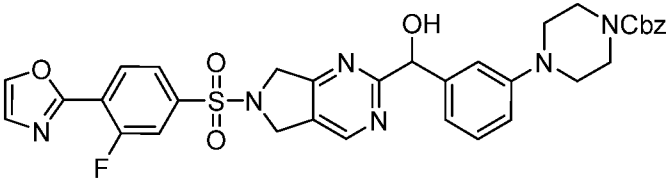
[0095] To a solution of 4-(1H-imidazol-1-yl)benzene-1-sulfonyl chloride (200 mg, 0.82 mmol) in DCM (2 mL) was added 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine (124 mg, 0.55 mmol) and TEA (0.22 mL, 1.60 mmol). The resulting solution was stirred for 2 h at 25 °C. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 1-[4-({6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl}phenyl]-1H-imidazole as a white solid (95 mg, 22%). LCMS (ES, m/z) 431 $[M+H]^+$.

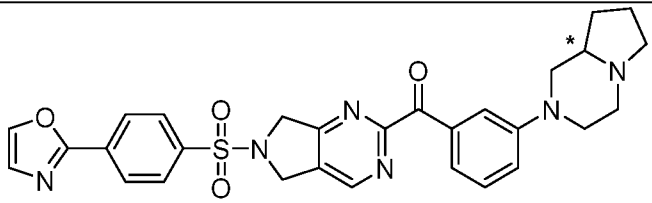
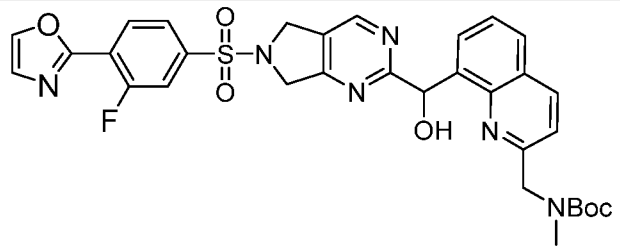
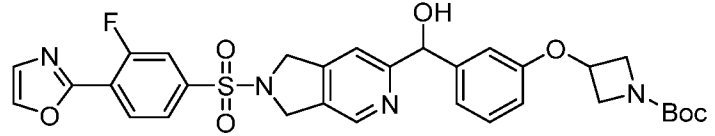
[0096] The Intermediates in Table 6 were synthesized according to the procedure described for Intermediate 8-1 above.

Table 6.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
8-2	 (3-[2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl]phenyl)methyl N-methylcarbamate	586
8-3	 Benzyl N-(2-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl}-2-phenylethyl)-N-methylcarbamate	612
8-4	 (3-bromophenyl)([2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl])methanol	529, 531
8-5	 (2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanone	432
8-6	 (2-((3-fluoro-4-(1H-pyrazol-1-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanone	449
8-7	 (2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanone	423

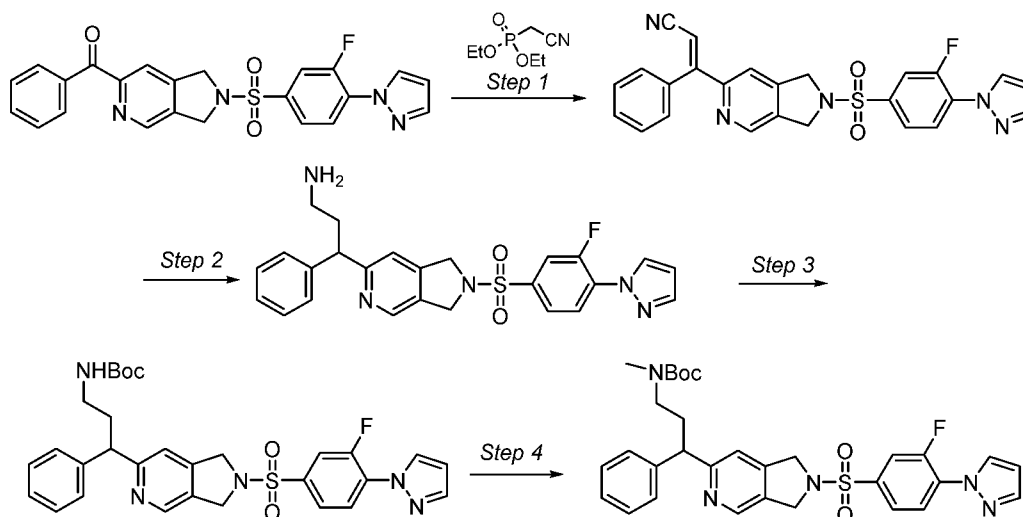
Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
8-8	 tert-butyl 4-((6-(hydroxy(phenyl)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl)piperidine-1-carboxylate	474
8-9	 (3-chlorophenyl)(2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanone	459
8-10	 6-chloro-2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine	353
8-11	 (3-bromophenyl)(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol	512, 514
8-12	 ethyl 4-((6-benzoyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl)piperidine-1-carboxylate	444
8-13	 (2-((4-(1H-pyrazol-1-yl)cyclohexyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanone	437
8-14	 (3-bromophenyl)(2-((4-(5-fluoroxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol	530, 532

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
	(3-bromophenyl)(2-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol	
8-15	 benzyl 4-(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carbonyl)isoindoline-2-carboxylate	607
8-16	 (6-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-(4-methylpiperazin-1-yl)phenyl)methanone	549
8-17	 2-(4-((6-((3-bromophenyl)(methoxy)methyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl)phenyl)oxazole	526, 528
8-18	 (4-methyl-3-(4-methylpiperazin-1-yl)phenyl)(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanone	544
8-19	 benzyl 4-(3-((6-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(hydroxy)methyl)phenyl)piperazine-1-carboxylate	537

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
8-20	 (3-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)(6-((4-(oxazol-2-yl)phenyl)sulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)methanone	557
8-21	 tert-butyl ((8-((6-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(hydroxy)methyl)quinolin-2-yl)methyl)(methyl)carbamate	647
8-22	 tert-butyl 3-(3-((2-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(hydroxy)methyl)phenoxy)azetidine-1-carboxylate	623

*Absolute stereochemistry is not determined.

Intermediate 9-1. Tert-butyl N-(3-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl] -1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl} -3-phenylpropyl)-N-methylcarbamate



Step 1. 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]-3-phenylprop-2-enitrile

[0097] To a solution of diethyl (cyanomethyl)phosphonate (65 mg, 0.37 mmol) in N,N-dimethylformamide (3 mL) was added sodium hydride (20 mg, 0.83 mmol, 60% dispersion in mineral oil) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. This was followed by addition of a solution of 1-[4-([6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl]-2-fluorophenyl]-1H-pyrazole (110 mg, 0.25 mmol) in DMF (1 mL). The resulting solution was stirred for 1 h at room temperature. The reaction mixture was poured into saturated ammonium chloride solution (5 mL) and then extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 1:1 ethyl acetate/petroleum ether) to afford 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]-3-phenylprop-2-enitrile as light yellow oil (90 mg, 78%). LCMS (ES, m/z) 472 [M+H]⁺.

Step 2. 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]-3-phenylpropan-1-amine

[0098] To a solution of 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]-3-phenylprop-2-enitrile (90 mg, 0.19 mmol) in methanol (2 mL) was added palladium carbon (10 mg, 10wt% palladium on charcoal). Then hydrogen was introduced with hydrogen balloon. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was filtered and concentrated under vacuum to afford 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]-3-phenylpropan-1-amine as yellow oil (50 mg, 55%). LCMS (ES, m/z) 478 [M+H]⁺.

Step 3. Tert-butyl N-(3-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl}-3-phenylpropyl)carbamate

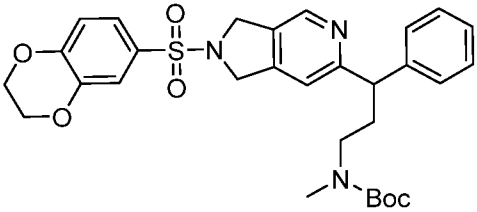
[0099] To a solution of 3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-3-phenylpropan-1-amine (50 mg, 0.10 mmol) in dichloromethane (1 mL) was added TEA (32 mg, 0.32 mmol) and di-tert-butyl dicarbonate (46 mg, 0.21 mmol). The resulting solution was stirred for 2 h at room temperature and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 2:1 ethyl acetate/petroleum ether) to afford tert-butyl N-(3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-3-phenylpropyl)carbamate as light yellow oil (40 mg, 66%). LCMS (ES, m/z) 578 [M+H]⁺.

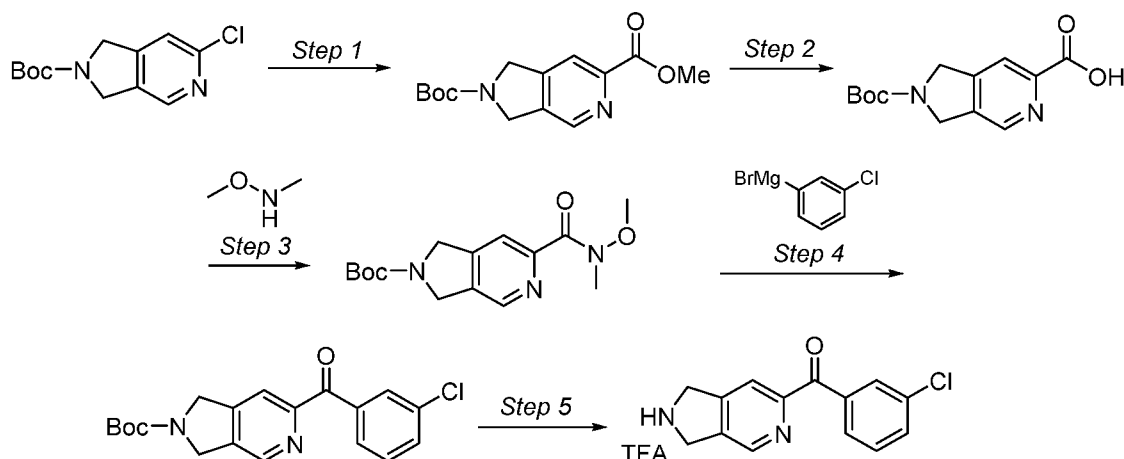
Step 4. Tert-butyl N-(3-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl}-3-phenylpropyl)-N-methylcarbamate

[0100] To a solution of tert-butyl N-(3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-3-phenylpropyl)carbamate (40 mg, 0.07 mmol) in tetrahydrofuran (1 mL) was added sodium hydride (6 mg, 0.15 mmol, 60% dispersion in mineral oil) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C. This was followed by the addition of iodomethane (15 mg, 0.11 mmol). The resulting solution was stirred for 16 h at room temperature. The reaction mixture was poured into saturated NH₄Cl (2 mL) and then extracted with ethyl acetate (3x3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 2:1 ethyl acetate/petroleum ether) to afford tert-butyl N-(3-[2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-3-phenylpropyl)-N-methylcarbamate as light yellow oil (30 mg, 73%). LCMS (ES, m/z) 592 [M+H]⁺.

[0101] The Intermediates in Table 7 were synthesized according to the procedure described for Intermediate 9-1 above.

Table 7.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
9-2	 tert-butyl (3-(2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)-3-phenylpropyl)(methyl)carbamate	566

Intermediate 10-1. 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine (TFA salt)**Step 1. 2-tert-butyl 6-methyl 1H,2H,3H-pyrrolo[3,4-c]pyridine-2,6-dicarboxylate**

[0102] Into a high pressure tank was placed a solution of tert-butyl 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2 g, 6.99 mmol) in MeOH (30 mL), Pd(dppf)Cl₂·CH₂Cl₂ (640 mg, 0.78 mmol) and TEA (3.28 mL, 23.7 mmol). Then CO (30 atm) was introduced. The resulting mixture was stirred for 16 h at 120 °C and cooled to room temperature. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:5 EA/PE) to afford 2-tert-butyl 6-methyl 1H,2H,3H-pyrrolo[3,4-c]pyridine-2,6-dicarboxylate as a yellow solid (1.2 g, 56%). LCMS (ES, m/z) 279 [M+H]⁺.

Step 2. 2-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid

[0103] To a solution of 2-tert-butyl 6-methyl 1H,2H,3H-pyrrolo[3,4-c]pyridine-2,6-dicarboxylate (2 g, 6.47 mmol) in THF (20 mL) was added water (15 mL) and LiOH (863 mg, 36.0 mmol). The resulting solution was stirred for 16 h at rt. The resulting mixture was washed with Et₂O (1 x 10 mL) and then acidified to pH 5 with hydrochloric acid solution (2 N). The resulting mixture was extracted with EA (3 x 25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by reversed phase chromatography (eluting with 1:1 water/MeCN). The collected fractions were combined and concentrated under vacuum to afford 2-(tert-butoxycarbonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-6-carboxylic acid as yellow oil (1.0 g, 53%). LCMS (ES, m/z) 265 [M+H]⁺.

Step 3. Tert-butyl 6-[methoxy(methyl)carbamoyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0104] To a solution of 2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carboxylic acid (1 g, 3.41 mmol) in DMF (15 mL) was added methoxy(methyl)amine hydrochloride (441 mg,

4.52 mmol), HATU (2.88 g, 7.57 mmol) and DIEA (1.98 mL, 11.37 mmol). The resulting solution was stirred for 1 h at rt. The reaction mixture was poured into water (15 mL) and then extracted with EA (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrate under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:10 EA/PE) to afford tert-butyl 6-[methoxy(methyl)carbamoyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (700 mg, 67%). LCMS (ES, m/z) 308 [M+H]⁺.

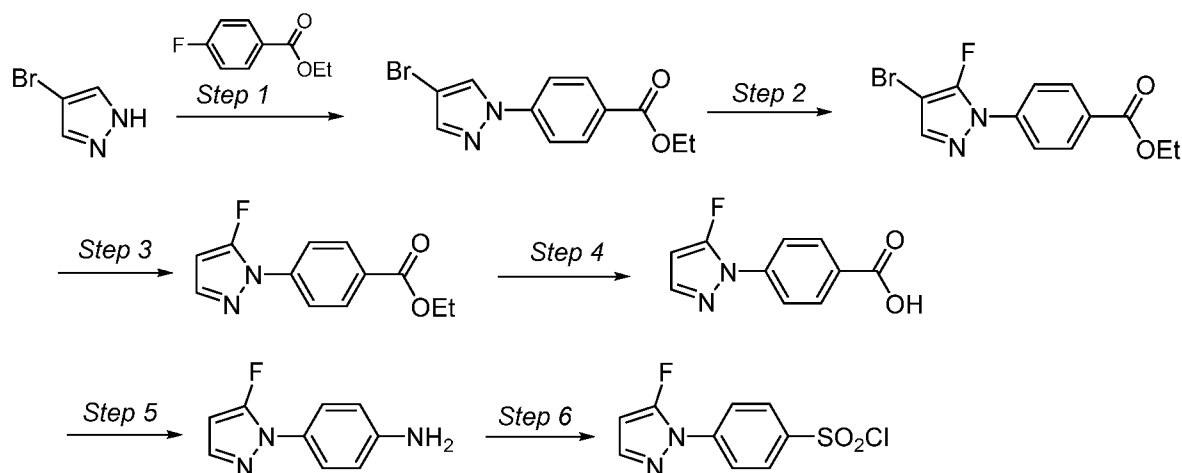
Step 4. Tert-butyl 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0105] To a solution of tert-butyl 6-[methoxy(methyl)carbamoyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (100 mg, 0.29 mmol) in THF (1 mL) was added a solution of bromo(3-chlorophenyl)magnesium (0.78 mL, 0.5 M in THF) dropwise with stirring at 0 °C. The resulting solution was stirred for 1 h at rt and then poured into saturated ammonium chloride solution (5 mL). The resulting mixture was extracted with EA (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:3 EA/PE) to afford tert-butyl 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as yellow oil (80 mg, 76%). LCMS (ES, m/z) 359, 361 [M+H]⁺.

Step 5. 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine TFA salt

[0106] To a solution of tert-butyl 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (500 mg, 1.25 mmol) in dichloromethane (8 mL) was added TFA (2 mL). The resulting solution was stirred for 1 h at rt. The resulting mixture was concentrated under vacuum to afford 6-[(3-chlorophenyl)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine (TFA salt) as brown oil (500 mg, crude). LCMS (ES, m/z) 259, 261 [M+H]⁺.

Intermediate 11-1. 4-(5-fluoro-1H-pyrazol-1-yl) benzene-1-sulfonyl chloride



Step 1. Ethyl 4-(4-bromo-1H-pyrazol-1-yl) benzoate

[0107] To a solution of 4-bromo-1H-pyrazole (10 g, 68.0 mmol) in N,N-dimethylformamide (100 mL) was added ethyl 4-fluorobenzoate (12 g, 85.1 mmol), and potassium carbonate (29 g, 210 mmol). The resulting mixture was stirred for 16 h at 120 °C and then cooled to room temperature. The reaction mixture was poured into water (80 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 40:60 ethyl acetate/petroleum ether) to afford ethyl 4-(4-bromo-1H-pyrazol-1-yl) benzoate (7 g, 38%). LCMS (ES, m/z) 295, 297 [M+H]⁺.

Step 2. Ethyl 4-(4-bromo-5-fluoro-1H-pyrazol-1-yl) benzoate

[0108] To a solution of ethyl 4-(4-bromo-1H-pyrazol-1-yl) benzoate (7 g, 23.7 mmol) in MeCN (70 mL) was added SelectFluor (26 g, 73.4 mmol). The resulting mixture was stirred for 48 h at 80 °C and then cooled to room temperature. The reaction mixture was poured into water (40 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 38:62 ethyl acetate/petroleum ether) to afford ethyl 4-(4-bromo-5-fluoro-1H-pyrazol-1-yl) benzoate (2.5 g, 34%). LCMS (ES, m/z) 313, 315 [M+H]⁺.

Step 3. Ethyl 4-(5-fluoro-1H-pyrazol-1-yl) benzoate

[0109] To a solution of ethyl 4-(4-bromo-5-fluoro-1H-pyrazol-1-yl) benzoate (2.50 g, 7.98 mmol) in ethyl acetate (50 mL) was added palladium carbon (250 mg, 10wt% palladium on charcoal). Then hydrogen was introduced in with hydrogen balloon. The resulting mixture was stirred for 1 h at room temperature, then filtered and concentrated under vacuum to afford ethyl 4-(5-fluoro-1H-pyrazol-1-yl)benzoate (800 mg, 43%). LCMS (ES, m/z) 235 [M+H]⁺.

Step 4. 4-(5-fluoro-1H-pyrazol-1-yl) benzoic acid

[0110] To a solution of ethyl 4-(5-fluoro-1H-pyrazol-1-yl)benzoate (800 mg, 3.42 mmol) in THF (4 mL) was added water (4 mL) and lithium hydroxide (411 mg, 17.2 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was washed with diethyl ether (1 x 6 mL) and then acidified to pH 5 with hydrochloric acid (4 N). The resulting solution was extracted with ethyl acetate (2 x 6 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford 4-(5-fluoro-1H-pyrazol-1-yl)benzoic acid (600 mg, 85%). LCMS (ES, m/z) 207 [M+H]⁺.

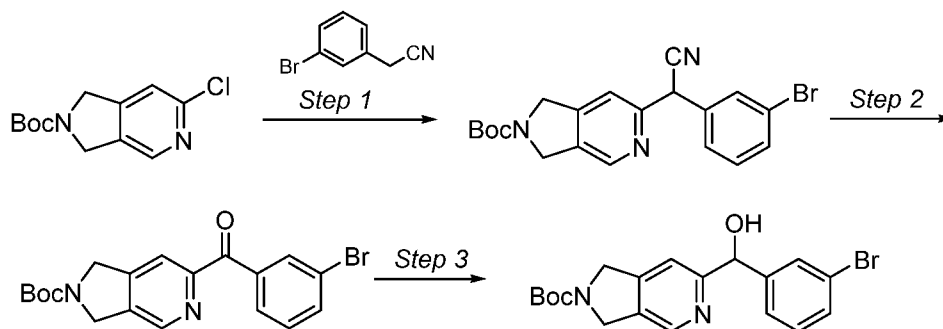
Step 5. 4-(5-fluoro-1H-pyrazol-1-yl) aniline

[0111] To a solution of 4-(5-fluoro-1H-pyrazol-1-yl) benzoic acid (500 mg, 2.43 mmol) in DMF (10 mL) was added TEA (1.0 mL, 7.28 mmol), and diphenylphosphoryl azide (1.0 g, 3.63 mmol). The resulting solution was stirred for 3 h at room temperature. To this was added a solution of sulfuric acid (3 mL, 1 M in water). The resulting solution was stirred for 1 h at 100 °C and then cooled to room temperature. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 4-(5-fluoro-1H-pyrazol-1-yl) aniline (400 mg, 93%). LCMS (ES, m/z) 178 [M+H]⁺.

Step 6. 4-(5-fluoro-1H-pyrazol-1-yl) benzene-1-sulfonyl chloride

[0112] To glacial acetic acid (10 mL) was bubbled SO₂ gas for 1 h at room temperature. Then CuCl₂ (72 mg, 0.54 mmol) was added and SO₂ gas was bubbled in for additional 2 h to afford solution A. To a pre-cooled solution of 4-(5-fluoro-1H-pyrazol-1-yl)aniline (380 mg, 2.14 mmol) in acetic acid (2 mL) and concentrated hydrochloric acid (6 mL) was added a solution of sodium nitrite (163 mg, 2.36 mmol) in distilled water (0.5 mL) dropwise with stirring at -10 °C. After stirring for 15 min, solution A was added to this diazonium salt solution at -10 °C. The resulting solution was allowed to warm to room temperature naturally and stirred for 16 h. The reaction mixture was treated with water (10 mL) and then extracted with EA (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 12:88 ethyl acetate/petroleum ether) to afford 4-(5-fluoro-1H-pyrazol-1-yl) benzene-1-sulfonyl chloride (350 mg, 63%). LCMS (ES, m/z) 261, 263 [M+H]⁺.

Intermediate 12-1. Tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate



Step 1. Tert-butyl 6-[(3-bromophenyl)(cyano)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0113] To a solution of tert-butyl 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.0 g, 7.79 mmol) in tetrahydrofuran (20 mL) was added NaNH₂ (2.0 g, 7.87 mmol), and 2-(3-bromophenyl)acetonitrile (2.32 g, 11.8 mmol). The resulting mixture was stirred for 16 h at 50 °C and then cooled to room temperature. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-[(3-bromophenyl)(cyano)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (1.1 g, 34 %). LCMS (ES, *m/z*) 414, 416 [M+H]⁺.

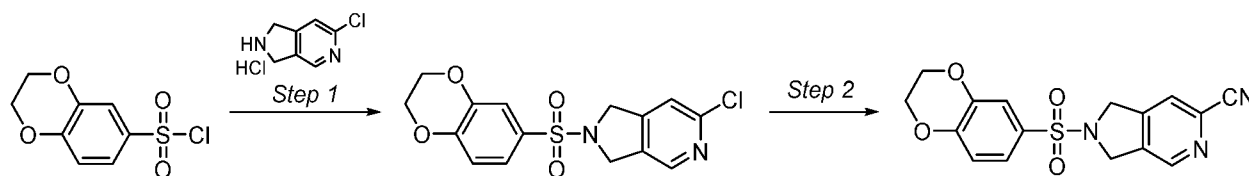
Step 2. Tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0114] To a solution of sodium hydroxide (128 mg, 0.012 mmol) in water (0.13 mL) was added DMSO (8 mL), benzyltriethylammonium chloride (27 mg, 0.12 mmol) and a solution of tert-butyl 6-[(3-bromophenyl)(cyano)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (1.1 g, 2.66 mmol) in DMSO (10 mL). The resulting solution was stirred for 3 h at room temperature while oxygen was bubbling in. The reaction mixture was poured into water (20 mL) and then extracted with EA (3 x 20 mL). The combined organic layers were washed by brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (640 mg, 60%). LCMS (ES, *m/z*) 403, 405 [M+H]⁺.

Step 3. Tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0115] To a solution of tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (500 mg, 1.24 mmol) in tetrahydrofuran (10 mL) was added NaBH₄ (95 mg, 2.49 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was poured into water (10 mL) and then extracted with EA (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 25:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (400 mg, 80%). LCMS (ES, *m/z*) 405, 407 [M+H]⁺.

Intermediate 13-1. 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile



Step 1. 6-chloro-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine

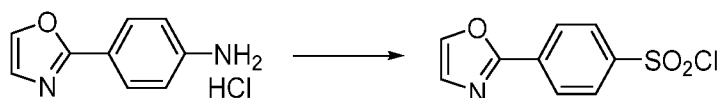
[0116] To a solution of 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine hydrochloride (810 mg, 4.24 mmol) in dichloromethane (10 mL) was added triethylamine (1.78 mL). This was followed by the addition of a solution of 2,3-dihydro-1,4-benzodioxine-6-sulfonyl chloride (1.00 g, 4.26 mmol) in dichloromethane (1 mL) dropwise with stirring at 0 °C. The resulting mixture was stirred for 2 h at rt. The reaction mixture was poured into water (10 mL) and then extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 6-chloro-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine (1 g, 60%). LCMS (ES, *m/z*) 353, 355 [M+H]⁺.

Step 2. 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile

[0117] To a solution of 6-chloro-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine (350 mg, 0.89 mmol) in N,N-dimethylformamide (3 mL) was added Zn(CN)₂ (173 mg, 1.47 mmol), and Pd(PPh₃)₄ (115 mg, 0.10 mmol). The resulting mixture was stirred for 1 h at 120 °C and then cooled to room temperature. The reaction mixture was poured into water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was

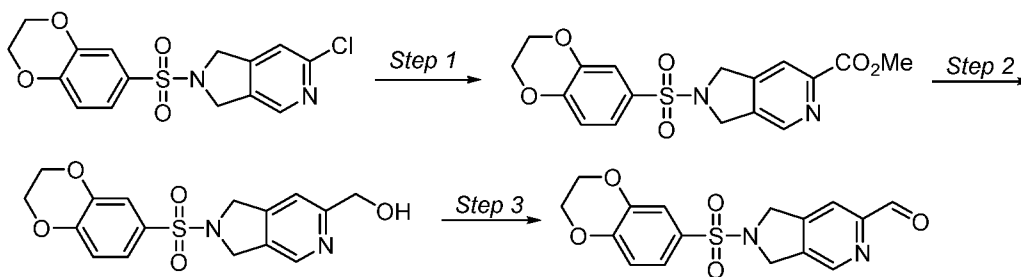
purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile as a white solid (285 mg 84%) LCMS (ES, m/z) 344 $[M+H]^+$.

Intermediate 14-1. 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride



[0118] To glacial acetic acid (20 mL) was bubbled SO_2 gas for 1 h at room temperature. Then $CuCl_2$ (256 mg, 1.91 mmol) was added and SO_2 gas was bubbled in for additional 2 h to afford solution A. To a pre-cooled solution of 4-(1,3-oxazol-2-yl)aniline hydrochloride (1.5 g, 7.65 mmol) in acetic acid (5 mL) and concentrated hydrochloric acid (15 mL) was added a solution of sodium nitrite (581mg, 8.42 mmol) in distilled water (2 mL) dropwise with stirring at $-10\text{ }^\circ\text{C}$. After stirring for 15 min, solution A was added to this diazonium salt solution at $-10\text{ }^\circ\text{C}$. The resulting solution was allowed to warm to room temperature naturally and stirred for 16 h. The reaction mixture was treated with water (20 mL) and then extracted with EA (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:70 ethyl acetate/petroleum ether) to afford 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride as a white solid (1.3 g, 70%). LCMS (ES, m/z) 244, 246 $[M+H]^+$.

Intermediate 15-1. 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbaldehyde



Step 1. Methyl 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carboxylate

[0119] Into a high pressure tank was placed a solution of 6-chloro-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine (200 mg, 0.54 mmol) in MeOH (5 mL), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (23 mg, 0.03 mmol) and TEA (0.24 mL, 1.70 mmol). Then CO (30 atm) was introduced. The resulting mixture was stirred for 5 h at $100\text{ }^\circ\text{C}$ and cooled to room temperature. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was

purified by silica gel chromatography (eluting with 10:1 DCM/MeOH) to afford methyl 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carboxylate as a yellow solid (160 mg, 79%). LCMS (ES, m/z) 377 [M+H]⁺.

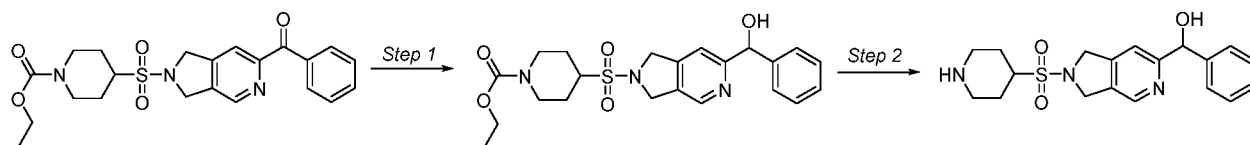
Step 2. [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol

[0120] To a solution of methyl 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carboxylate (200 mg, 0.50 mmol) in THF (5 mL) was added LiAlH₄ (10 mg, 0.26 mmol) carefully with stirring at 0 °C. The resulting solution was stirred for 20 min at 0 °C. The reaction was then quenched by addition of Na₂SO₄·10H₂O (100 mg). The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 10:1 DCM/MeOH) to afford [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol as a yellow solid (160 mg, 91%). LCMS (ES, m/z) 349 [M+H]⁺.

Step 3. 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbaldehyde

[0121] To a solution of [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol (80 mg, 0.21 mmol) in 1,4-dioxane (3 mL) was added SeO₂ (13 mg, 0.12 mmol). The resulting mixture was stirred for 16 h at 80 °C and then cooled to room temperature. The reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 EA/PE) to afford 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbaldehyde as yellow oil (40 mg, 56%). LCMS (ES, m/z) 347 [M+H]⁺.

Intermediate 16-1. Phenyl[2-(piperidine-4-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]methanol



Step 1. Ethyl 4-((6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-yl)sulfonyl)piperidine-1-carboxylate

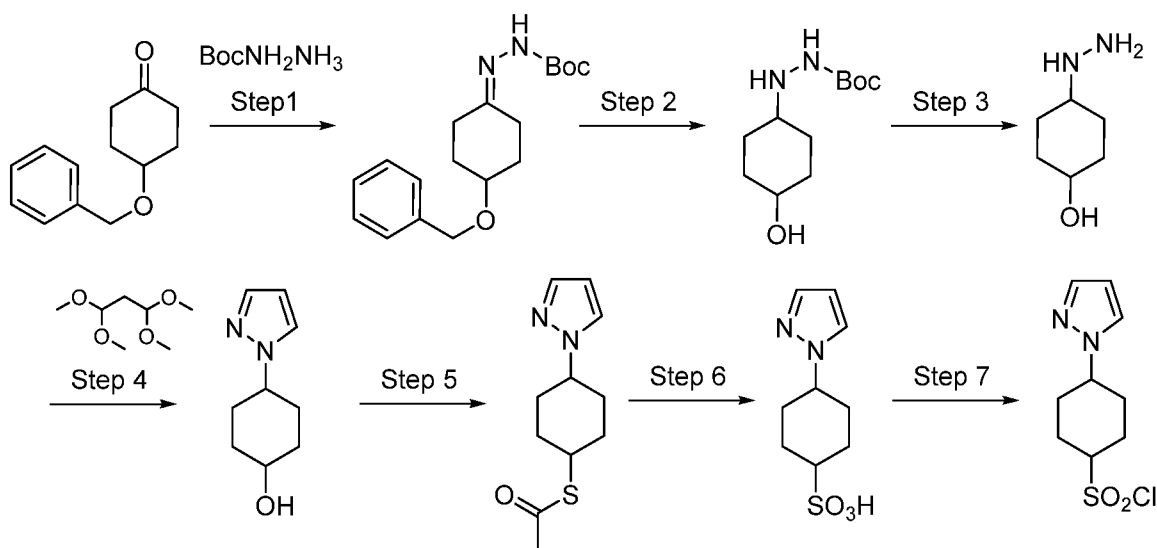
[0122] To a solution of ethyl 4-([6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl)sulfonyl)piperidine-1-carboxylate (200 mg, 0.45 mmol) in methanol (4 mL), was added sodium borohydride (34 mg, 0.90 mmol). The resulting solution was stirred for 1 h at room temperature. The

reaction mixture was poured into water (5 mL) and then extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 70:30 ethyl acetate/petroleum ether) to afford ethyl 4-([6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-yl]sulfonyl)piperidine-1-carboxylate as light yellow oil (180 mg, 90%). LCMS (ES, m/z) 446 [M+H]⁺.

Step 2. Phenyl[2-(piperidine-4-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]methanol

[0123] To a solution of ethyl 4-([6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl] sulfonyl)piperidine-1-carboxylate (170 mg, 0.38 mmol) in tetrahydrofuran (2 mL) was added methanol (2 mL), water (2 mL) and sodium hydroxide (78 mg, 1.95 mmol). The resulting solution was stirred for 16 h at 65 °C. The reaction mixture was poured into water (2 mL) and then extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 methanol/dichloromethane) to afford phenyl[2-(piperidine-4-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol as yellow oil (90 mg, 63%). LCMS (ES, m/z) 374 [M+H]⁺.

Intermediate 17-1. 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonyl chloride



Step 1. N'-[4-(benzyloxy)cyclohexylidene](tert-butoxy)carbohydrazide

[0124] To a solution of 4-(benzyloxy)cyclohexan-1-one (5 g, 0.025 mol) in methanol (25 mL) was added (tert-butoxy)carbohydrazide (3.2 g, 0.025 mol). The resulting solution was stirred for 1 h at rt. The resulting mixture was concentrated to minimum volume, filtered and dried under vacuum to afford

N-4-(benzyloxy)cyclohexylidene](tert-butoxy)carbohydrazide as a yellow solid (3 g, 35%). 319 [M+H]⁺.

Step 2. N'-(4-hydroxycyclohexyl)(tert-butoxy)carbohydrazide

[0125] To a solution of N-4-(benzyloxy)cyclohexylidene](tert-butoxy)carbohydrazide (3 g, 8.95 mmol) in methanol (300 mL) was added palladium carbon (300 mg, 10 wt% palladium on charcoal). Then hydrogen was introduced with hydrogen balloon. The resulting solution was stirred for 16 h at rt. The solids were filtered out. The filtrate was concentrated under vacuum to afford N'-(4-hydroxycyclohexyl)(tert-butoxy)carbohydrazide as yellow oil (2 g, 87%). LCMS (ES, *m/z*) 231 [M+H]⁺.

Step 3. 4-hydrazinylcyclohexan-1-ol hydrochloride

[0126] To a solution of N'-(4-hydroxycyclohexyl)(tert-butoxy)carbohydrazide (2 g, 7.82 mmol) in dichloromethane (50 mL) was added a solution of hydrochloric acid (5 mL, 4 N in 1,4-dioxane). The resulting solution was stirred for 3 h at rt. The resulting mixture was concentrated under vacuum to afford 4-hydrazinylcyclohexan-1-ol hydrochloride as yellow oil (1.1 g, 85%). LCMS (ES, *m/z*) 131 [M+H]⁺.

Step 4. 4-(1H-pyrazol-1-yl)cyclohexan-1-ol

[0127] To a solution of 4-hydrazinylcyclohexan-1-ol hydrochloride (1.8 g, 9.72 mmol) in ethanol (100 mL) was added 1,1,3,3-tetramethoxypropane (1.94 g, 11.8 mmol). The resulting mixture was stirred for 2 h at 90 °C and then cooled to room temperature. The resulting mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford 4-(1H-pyrazol-1-yl)cyclohexan-1-ol as yellow oil (1.2 g, 67%). LCMS (EI, *m/z*): 167 [M+H]⁺.

Step 5. 1-[[4-(1H-pyrazol-1-yl)cyclohexyl]sulfanyl]ethan-1-one

[0128] To a solution of triphenylphosphine (4.1 g, 15.6 mmol) in tetrahydrofuran (10 mL) was added diisopropyl azodicarboxylate (3.2 g, 15.6 mmol) dropwise with stirring at -10 °C. To this was added a solution of 4-(1H-pyrazol-1-yl)cyclohexan-1-ol (1.3 g, 7.8 mmol) in tetrahydrofuran (3 mL) dropwise with stirring at -10 °C and ethanethioic S-acid (1.2 g, 15.6 mmol). The resulting solution was stirred for 16 h at rt. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 5:95 ethyl acetate/petroleum ether) to afford 1-[[4-(1H-

pyrazol-1-yl)cyclohexyl)sulfanyl}ethan-1-one as yellow oil (700 mg, 36%). LCMS (ES, m/z) 225 $[M+H]^+$.

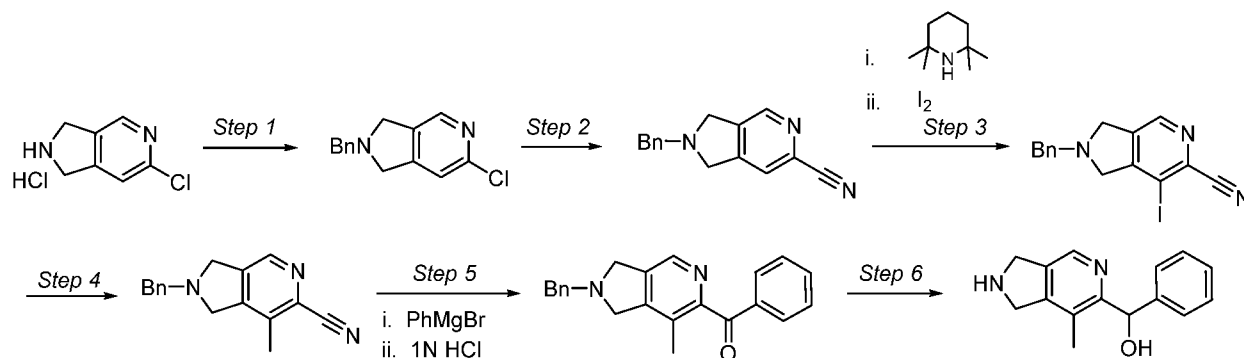
Step 6. 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonic acid

[0129] To a solution of 1-[[4-(1H-pyrazol-1-yl)cyclohexyl)sulfanyl]ethan-1-one (550 mg, 2.21 mmol) in formic acid (11 mL) and hydrogen peroxide (1.2 mL). The resulting solution was stirred for 2 h at room temperature. The resulting mixture was concentrated under vacuum to afford 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonic acid as a white solid (400 mg, 71%). LCMS (ES, m/z) 231 $[M+H]^+$.

Step 7. 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonyl chloride

[0130] To a solution of 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonic acid (400 mg, 1.74 mmol) in DCM (100 mL) was added oxalyl dichloride (0.74 mL, 8.69 mmol) dropwise with stirring at 0 °C. The resulting mixture was stirred for 1 h at 0 °C and then concentrated under vacuum to afford 4-(1H-pyrazol-1-yl)cyclohexane-1-sulfonyl chloride as a yellow oil (400 mg, 93%).

Intermediate 18-1. {7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol



Step 1. 2-Benzyl-6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine

[0131] To a solution of 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine hydrochloride (1.20 g, 6.28 mmol) in MeOH (40 mL) was added triethylamine (0.87 mL, 6.29 mmol) and benzaldehyde (800 mg, 7.54 mmol). The resulting solution was stirred for 30 min at rt. Then sodium triacetoxyborohydride (3.90 g, 18.8 mmol) was added. The resulting solution was stirred for 16 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 2-benzyl-6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine as colorless oil (480 mg, 31%). LCMS (ES, m/z): 245, 247 $[M+H]^+$.

Step 2. 2-Benzyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile

[0132] To a solution of 2-benzyl-6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine (480 mg, 1.96 mmol) in DMF (8 mL) was added Zn(CN)₂ (461 mg, 3.93 mmol), and Pd(dppf)Cl₂ (144 mg, 0.20 mmol). The resulting mixture was irradiated with microwave for 3 h at 140 °C. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 2-benzyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile as a white solid (300 mg, 65%). LCMS (ES, m/z): 236 [M+H]⁺.

Step 3. 2-Benzyl-7-iodo-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile

[0133] To a solution of 2,2,6,6-tetramethylpiperidine (461 mg, 3.26 mmol) in tetrahydrofuran (10 mL) was added n-BuLi (1.2 mL, 2.5 M in THF) at -78 °C. The resulting solution was stirred for 30 min. Then a solution of 2-benzyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile (480 mg, 2.04 mmol) in THF (5 mL) was added and stirred for 30 min at -78 °C. After that a solution of diiodine (828 mg, 3.26 mmol) in THF (5 mL) was added. The resulting solution was stirred for 30 min at -78 °C and then allowed to warm to room temperature naturally. The reaction mixture was poured into saturated ammonium chloride (20 mL) and then extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 2-benzyl-7-iodo-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile as a yellow solid (611 mg, 83%). LCMS (ES, m/z): 362 [M+H]⁺.

Step 4. 2-Benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile

[0134] To a solution of 2-benzyl-7-iodo-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile (611 mg, 1.69 mmol) in 1,4-dioxane (20 mL) was added Sn(CH₃)₄ (605 mg, 3.38 mmol), and Pd(dppf)Cl₂ (62 mg, 0.08 mmol). The resulting solution was stirred for overnight at 100 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 2-benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile as colorless oil (400 mg, 95%). LCMS (ES, m/z): 250 [M+H]⁺.

Step 5. 6-benzoyl-2-benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine

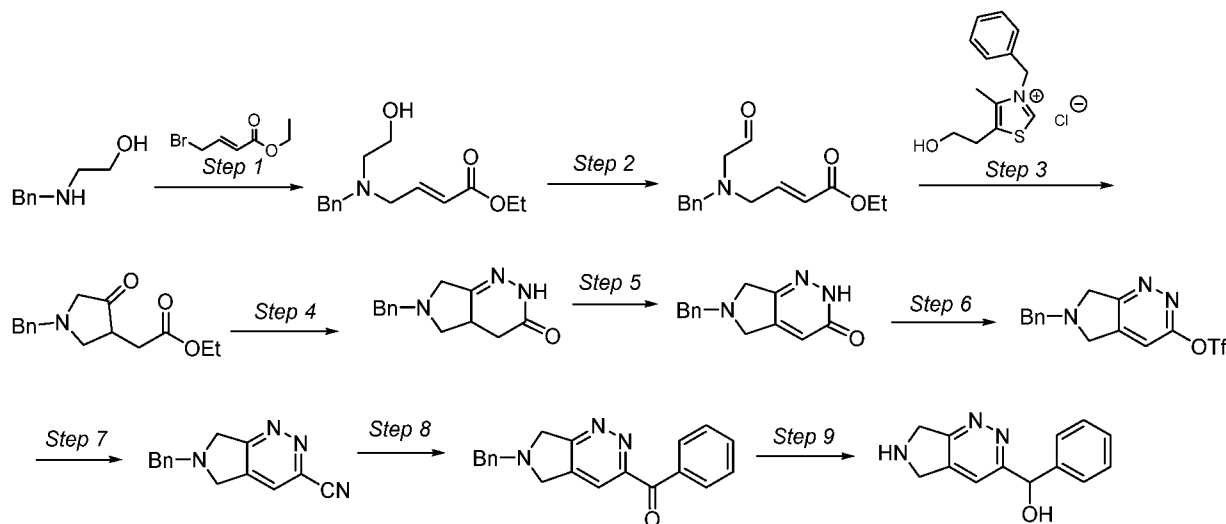
[0135] To a solution of 2-benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile (390 mg, 1.56 mmol) in tetrahydrofuran (15 mL) was added a solution of bromo(phenyl)magnesium (3.13 mL, 1 M in THF) at 0 °C. The resulting mixture was stirred for 16 h and hydrochloric acid (10 mL, 1

N) was added. The resulting solution was stirred for 30 min and poured into water (50 mL) and then extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 6-benzoyl-2-benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine as yellow oil (300 mg, 58%). LCMS (ES, m/z): 329 [M+H]⁺.

Step 6. {7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol

[0136] To a solution of 6-benzoyl-2-benzyl-7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine (150 mg, 0.46 mmol) in methanol (15 mL) was added Pd(OH)₂/C (150 mg, 20 wt% Pd). Then hydrogen was introduced in with hydrogen balloon. The resulting mixture was stirred for 2 h at rt. The reaction mixture was filtered and concentrated under vacuum to afford {7-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol as yellow oil, which was used directly in the next step without further purification (150 mg, crude). LCMS (ES, m/z) 241 [M+H]⁺.

Intermediate 19-1. Phenyl({5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl})methanol



Step 1. Ethyl 4-[benzyl(2-hydroxyethyl)amino]but-2-enoate

[0137] To a solution of 2-(benzylamino)ethan-1-ol (20.0 g, 133 mmol) in dichloromethane (150 mL), was added ethyl 4-bromobut-2-enoate (12.9 g, 66.8 mmol), potassium carbonate (18.5 g, 133 mmol). The resulting solution was stirred for 16 h at room temperature. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 25:75 ethyl acetate/petroleum ether) to afford ethyl 4-[benzyl(2-hydroxyethyl)amino]but-2-enoate as colorless oil (13.0 g, 74%). LCMS (ES, m/z): 264 [M+H]⁺.

Step 2. Ethyl 4-[benzyl(2-oxoethyl)amino]but-2-enoate

[0138] To a solution of oxalyl chloride (12.5 g, 98.7 mmol) in dichloromethane (150 mL) was added DMSO (10.5 mL, 148 mmol) dropwise at -78 °C. After stirring for 20 min, to this solution was added a solution of ethyl 4-[benzyl(2-hydroxyethyl)amino]but-2-enoate (13.0 g, 49.4 mmol) in dichloromethane (20 mL) dropwise at -78 °C. The resulting solution was stirred for 20 min and then triethylamine (41.0 mL, 0.29 mmol) was added. The resulting solution was allowed to warm to room temperature naturally and stirred for 12 h. The resulting solution was poured into saturated sodium bicarbonate solution (100 mL) and then extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with 0:100 to 25:75 ethyl acetate/petroleum ether) to afford ethyl 4-[benzyl(2-oxoethyl)amino]but-2-enoate as light yellow oil (12.5 g, 99%). LCMS (ES, m/z): 262 [M+H]⁺.

Step 3. Ethyl 2-(1-benzyl-4-oxopyrrolidin-3-yl) acetate

[0139] To a solution of ethyl (2E)-4-[benzyl(2-oxoethyl)amino]but-2-enoate (12.5 g, 47.8 mmol) in tetrahydrofuran (50 mL) was added potassium carbonate (1.30 g, 9.95 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazol-3-ium chloride (2.70 g, 9.95 mmol). The resulting solution was stirred for 16 h at room temperature. The reaction mixture was poured into water (60 mL) and then extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford ethyl 2-(1-benzyl-4-oxopyrrolidin-3-yl) acetate as light yellow oil (7.70 g, 62%). LCMS (ES, m/z): 262 [M+H]⁺.

Step 4. 6-Benzyl-2H,3H,4H,4aH,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one

[0140] To a solution of ethyl 2-(1-benzyl-4-oxopyrrolidin-3-yl) acetate (7.70 g, 29.5 mmol) in ethanol (50 mL), was added hydrazine monohydrate (1.30 mL, 26.5 mmol). The resulting solution was stirred for 2 h at 70 °C. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 methanol/dichloromethane) to afford 6-benzyl-2H,3H,4H,4aH,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one as a white solid (2.50 g, 37%). LCMS (ES, m/z): 230 [M+H]⁺.

Step 5. 6-Benzyl-2H,3H,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one

[0141] To a solution of 6-benzyl-2H,3H,4H,4aH,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one (2.50 g, 10.9 mmol) in MeCN (80 mL) was added CuCl₂ (2.9 g, 21.8 mmol). The resulting mixture was

stirred for 2 h at 80 °C. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 methanol /dichloromethane) to afford 6-benzyl-2H,3H,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one as a red solid (1.20 g, 48%). LCMS (ES, m/z): 228 [M+H]⁺.

Step 6. 6-Benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl trifluoromethanesulfonate

[0142] To a solution of 6-benzyl-2H,3H,5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-one (1.20 g, 5.28 mmol) in pyridine (15 mL) was added Tf₂O (1.9 g, 6.87 mmol) in a water/ice bath. Then the resulting solution was stirred for 2 h at 70 °C. After cooling to room temperature, the reaction mixture was concentrated and treated with hydrochloric acid (60 mL, 1 N). The resulting solution was extracted with ethyl acetate (3 x 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:70 ethyl acetate/petroleum ether) to afford 6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl trifluoromethanesulfonate as a green solid (1.00 g, 53%). LCMS (ES, m/z): 360 [M+H]⁺.

Step 7. 6-Benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine-3-carbonitrile

[0143] To a solution of 6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl trifluoromethanesulfonate (700 mg, 1.95 mmol) in N,N-dimethylformamide (15 mL) was added Zn(CN)₂ (252 mg, 2.15 mmol), Pd₂(dba)₃ (71 mg, 0.08 mmol) and dppf (108 mg, 0.20 mmol). The resulting mixture was stirred for 16 h at 100 °C. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine-3-carbonitrile as a light yellow solid (400 mg, 87%). LCMS (ES, m/z): 237 [M+H]⁺.

Step 8. 3-Benzoyl-6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine

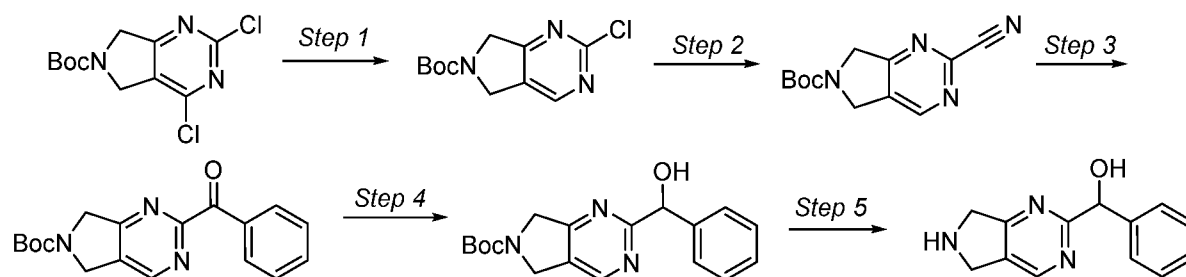
[0144] To a solution of 6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine-3-carbonitrile (100 mg, 0.42 mmol) in tetrahydrofuran (7 mL) was added bromo(phenyl)magnesium (0.21 mL, 3.0 M in THF) at 0 °C. The resulting solution was stirred for 2 h at room temperature. The reaction mixture was treated with hydrochloric acid (10 mL, 1 N) and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum.

The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 3-benzoyl-6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine as a white solid (100 mg, 75%). LCMS (ES, m/z): 316 $[M+H]^+$.

Step 9. Phenyl({5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl})methanol

[0145] To a solution of 3-benzoyl-6-benzyl-5H,6H,7H-pyrrolo[3,4-c]pyridazine (50 mg, 0.16 mmol) in methanol (7 mL) was added $Pd(OH)_2/C$ (8 mg, 20 wt% Pd) and several drops of hydrochloric acid (1 N). Then hydrogen was introduced with hydrogen balloon. The resulting mixture was stirred for 2 h at rt. The reaction mixture was filtered and concentrated under vacuum to afford phenyl({5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl})methanol as a white solid (30 mg, 36 %). LCMS (ES, m/z): 228 $[M+H]^+$.

Intermediate 20-1. Phenyl({5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol



Step 1. tert-Butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0146] To a solution of tert-butyl 2,4-dichloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (6.00 g, 17.6 mmol) in methanol (48 mL) was added zinc powder (1.80 g, 26.4 mmol) and acetic acid (10.6 mL, 176 mmol). The resulting mixture was stirred for 16 h at 50 °C and cooled to room temperature. The resulting mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:1 ethyl acetate/petroleum ether) to afford tert-butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a white solid (2.90 g, 54%). LCMS (ES, m/z): 256, 258 $[M+H]^+$.

Step 2. tert-Butyl 2-cyano-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0147] To a solution of tert-butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (1.50 g, 4.99 mmol) in DMF (15 mL) was added $Zn(CN)_2$ (868 mg, 7.48 mmol) and $Pd(dppf)Cl_2$ (364 mg, 0.50 mmol). The resulting mixture was irradiated with microwave for 3 h at 140 °C. After cooling to rt, the reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography

(eluting with 1:1 ethyl acetate/petroleum ether) to afford tert-butyl 2-cyano-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow oil (500 mg, 34%). LCMS (ES, m/z): 247 $[M+H]^+$.

Step 3. tert-Butyl 2-benzoyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0148] To a solution of tert-butyl 2-cyano-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (200 mg, 0.69 mmol) in THF (2 mL) was added bromo(phenyl)magnesium (1.38 mL, 1 M in THF) dropwise at 0 °C. The resulting mixture was stirred for 1 h at rt. Then 1 N hydrochloric acid (2 mL) was added. The resulting mixture was stirred for 30 min at rt and then extracted with EA (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 4:5 ethyl acetate/petroleum ether) to afford tert-butyl 2-benzoyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow oil (90 mg, 34%). LCMS (ES, m/z): 326 $[M+H]^+$.

Step 4. tert-Butyl 2-[hydroxy(phenyl)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

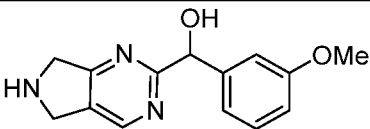
[0149] To a solution of tert-butyl 2-benzoyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (90 mg, 0.24 mmol) in methanol (1 mL) was added sodium borohydride (18.7 mg, 0.47 mmol). The resulting mixture stirred for 1 h at rt. The reaction mixture was poured into water (5 mL) and then extracted with EA (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-TLC (eluting with 2:5 ethyl acetate/petroleum ether) to afford tert-butyl 2-[hydroxy(phenyl)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (60 mg, 77%). LCMS (ES, m/z): 328 $[M+H]^+$.

Step 5. Phenyl({5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol

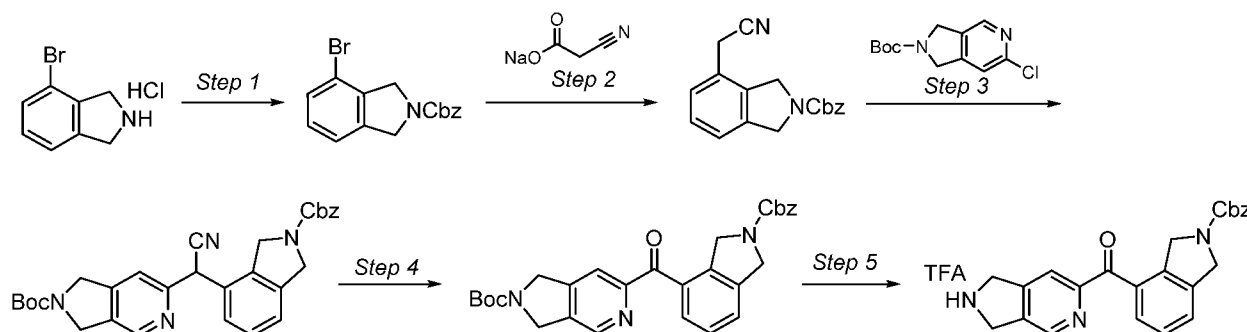
[0150] To a solution of tert-butyl 2-[hydroxy(phenyl)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (60 mg, 0.18 mmol) in DCM (6 mL) was added trifluoroacetic acid (2 mL). The resulting mixture was stirred for 1 h at rt and concentrated under vacuum. The resulting mixture was basified to pH 8 with saturated potassium carbonate solution and extracted with DCM (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to afford phenyl({5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol as a yellow solid (35 mg, 85%). LCMS (ES, m/z): 228 $[M+H]^+$.

[0151] The Intermediate in Table 8 were synthesized according to the procedure described for Intermediate 20-1 above.

Table 8.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
20-2	 (6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(3-methoxyphenyl)methanol	258

Intermediate 21-1. Benzyl 4-[1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]-2,3-dihydro-1H-isoindole-2-carboxylate



Step 1. Benzyl 4-bromo-2,3-dihydro-1H-isoindole-2-carboxylate

[0152] To a solution of 4-bromo-2,3-dihydro-1H-isoindole hydrochloride (3.00 g, 12.2 mmol) and TEA (5.10 mL, 36.5 mmol) in dichloromethane (50 mL) was added CbzCl (4.10 g, 24.3 mmol) in portions at 0 °C. The resulting solution was stirred for 5 h at room temperature. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford benzyl 4-bromo-2,3-dihydro-1H-isoindole-2-carboxylate as a pink solid (3.50 g, 87%). LCMS (ES, m/z): 332, 334[M+H]⁺.

Step 2. tert-Butyl 4-(cyanomethyl)-2,3-dihydro-1H-isoindole-2-carboxylate

[0153] To a solution of tert-butyl 4-bromo-2,3-dihydro-1H-isoindole-2-carboxylate (1.50 g, 4.78 mmol) in mesitylene (20 mL) was added Pd(allyl)₂Cl₂ (46 mg, 0.10 mmol), SPhos (118 mg, 0.29 mmol) and sodium 2-cyanoacetate (808 mg, 7.17 mmol). The resulting mixture was stirred for 5 h at 140 °C. After cooling to room temperature, the reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford tert-butyl 4-(cyanomethyl)-2,3-dihydro-1H-isoindole-2-carboxylate as a brown solid (1.00 g, 81%). LCMS (ES, m/z): 293[M+H]⁺.

Step 3. Benzyl 4-([2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](cyano)methyl)-2,3-dihydro-1H-isoindole-2-carboxylate

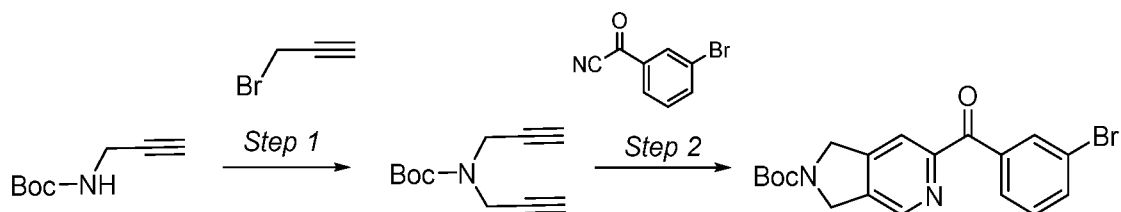
[0154] To a solution of tert-butyl 6-chloro-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (500 mg, 1.86 mmol) in THF (10 mL) was added benzyl 4-(cyanomethyl)-2,3-dihydro-1H-isoindole-2-carboxylate (861 mg, 2.80 mmol) and sodium amide (146 mg, 3.74 mmol). The resulting solution was stirred for 4 h at 50 °C. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:60 ethyl acetate/petroleum ether) to afford benzyl 4-([2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](cyano)methyl)-2,3-dihydro-1H-isoindole-2-carboxylate as yellow oil (300 mg, 32%). LCMS (ES, m/z): 511[M+H]⁺.

Step 4. Benzyl 4-([2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](cyano)methyl)-2,3-dihydro-1H-isoindole-2-carboxylate

[0155] To a solution of benzyl 4-([2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](cyano)methyl)-2,3-dihydro-1H-isoindole-2-carboxylate (300 mg, 0.56 mmol) in DMSO (5 mL) was added benzyltriethylammonium chloride (6 mg, 0.03 mmol) and sodium hydroxide (0.2 mL, 4 N in water). Then oxygen was bubbled in. The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford benzyl 4-[2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]-2,3-dihydro-1H-isoindole-2-carboxylate as yellow oil (200 mg, 72%). LCMS (ES, m/z): 500 [M+H]⁺.

Step 5. Benzyl 4-[1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]-2,3-dihydro-1H-isoindole-2-carboxylate (TFA salt)

[0156] To a solution of benzyl 4-[2-[(tert-butoxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]-2,3-dihydro-1H-isoindole-2-carboxylate (200 mg, 0.38 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL). The resulting solution was stirred for 5 h at room temperature. The resulting mixture was concentrated under vacuum to afford benzyl 4-[1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]-2,3-dihydro-1H-isoindole-2-carboxylate (TFA salt) as yellow oil (180 mg, crude). LCMS (ES, m/z): 400[M+H]⁺.

Intermediate 22-1. Tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate**Step 1. Tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate**

[0157] To a solution of tert-butyl N-(prop-2-yn-1-yl)carbamate (100 g, 612 mmol) in DMF (1.00 L), was added sodium hydride (29.4 g, 734 mmol, 60% dispersion in mineral oil) in portions with stirring at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. Then to the above mixture was added propargyl bromide (82.6 mL, 918 mmol). The resulting mixture was stirred for 16 h at 50 °C. After cooling to room temperature, the reaction mixture was poured into water (1 L) and then extracted with ethyl acetate (1.2 L x 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:15 ethyl acetate/petroleum ether) to afford tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate as yellow oil (90 g, 68%). LCMS (ES, m/z): 194 $[M+H]^+$.

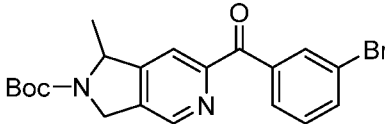
Step 2. Tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0158] To a solution of 3-bromobenzoyl cyanide (5.00 g, 22.6 mmol) in 1,2-dichloroethane (50 mL) was added $Cp^*Ru(COD)Cl$ (172 mg, 0.45 mmol) and tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (4.60 g, 22.6 mmol) at 0 °C. The resulting solution was stirred for 4 h at 60 °C. The reaction mixture was cooled to room temperature and then concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (6.30 g, 63%). LCMS (ES, m/z): 403,405 $[M+H]^+$.

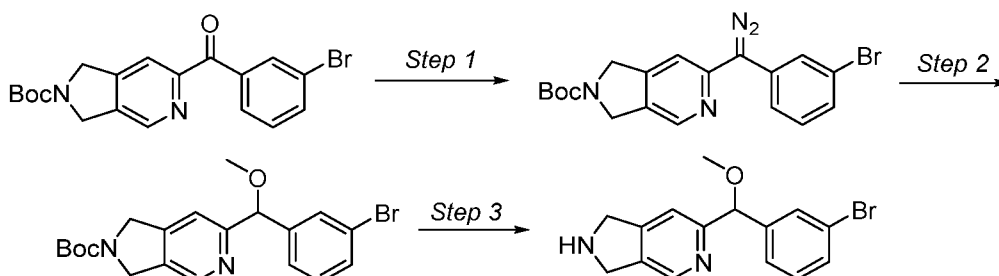
[0159] The Intermediates in Table 9 were synthesized according to the procedure described for Intermediate 22-1 above.

Table 9.

Intermediate	Compound	LCMS: (ESI) m/z $[M+H]^+$
22-2		417, 419

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
	tert-butyl 6-(3-bromobenzoyl)-3-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate 	
	tert-butyl 6-(3-bromobenzoyl)-1-methyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	

Intermediate 23-1. 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine



Step 3. Tert-butyl 6-[(3-bromophenyl)(diazo)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0160] To a solution of tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.20 g, 4.63 mmol) in MeOH (50 mL) was added 4-methylbenzene-1-sulfonylhydrazide (1.36 g, 6.95 mmol). The resulting mixture was stirred for 16 h at 60 °C. After cooling to room temperature, the reaction mixture was concentrated. The solids were collected by filtration and dried under vacuum to afford tert-butyl 6-[(3-bromophenyl)(diazo)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as an off-white solid (1.90 g, 60%). LCMS (EI, *m/z*): 415, 417 [M+H]⁺.

Step 4. Tert-butyl 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

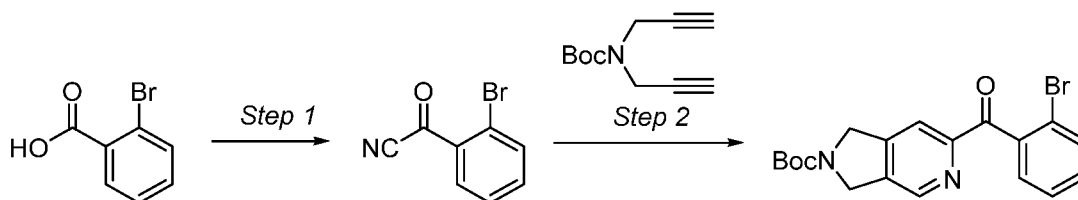
[0161] To a solution of tert-butyl 6-[(3-bromophenyl)(diazo)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (1.20 g, 2.45 mmol) in MeOH (20 mL) and 1,4-dioxane (20 mL) was added dirhodium tetraacetate (46 mg, 0.10 mmol). The resulting mixture was stirred for 16 h at 110 °C. After cooling to room temperature, the reaction mixture was poured into water (30 mL) and then extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate.

[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (900 mg, 72%). LCMS (ES, m/z): 419, 421 $[M+H]^+$.

Step 5. 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine

[0162] To a solution of tert-butyl 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (900 mg, 1.82 mmol) in DCM (5 mL) was added hydrochloric acid (5 mL, 4 N in 1,4-dioxane). The resulting solution was stirred for 2 h at room temperature. The reaction mixture was concentrated under vacuum to afford 6-[(3-bromophenyl)(methoxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine as a black solid (700 mg, 90%). LCMS (ES, m/z): 319, 321 $[M+H]^+$.

Intermediate 24-1. Tert-butyl 6-(2-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate



Step 1. 2-bromobenzoyl cyanide

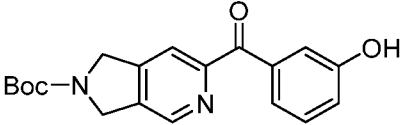
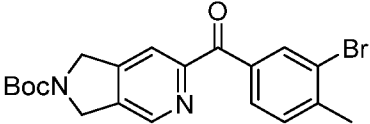
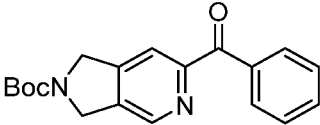
[0163] To 2-bromobenzoic acid (4.00 g, 18.9 mmol) was added oxalic dichloride (8.46 mL, 94.3 mmol). The resulting solution was stirred for 2 h at 25 °C. Then the reaction mixture was concentrated under vacuum. The resulting mixture was dissolved with MeCN (20 mL). To the above solution was added copper (I) cyanide (3.60 g, 37.8 mmol). The resulting mixture was stirred for 2 h at 85 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The resulting mixture was washed with diethyl ether (2 x 100 mL). The solids were filtered out. The filtrate was concentrated under vacuum. The resulting mixture was washed with hexane (2 x 100 mL). The solids were filtered out. The filtrate was concentrated under vacuum to afford 2-bromobenzoyl cyanide as a yellow solid (2.71 g, 62%).

Step 2. Tert-butyl 6-(2-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

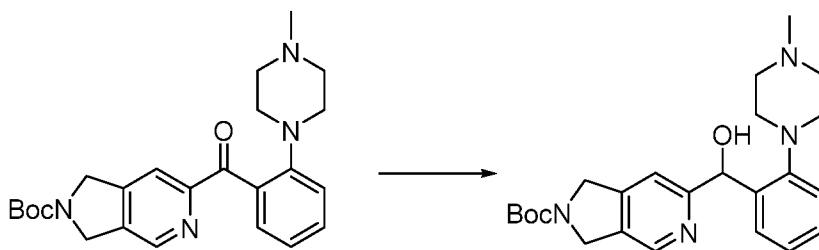
[0164] To a solution of 2-bromobenzoyl cyanide (2.20 g, 9.07 mmol) in DCE (25 mL) was added tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (2.50 g, 12.2 mmol), and Cp*₃Ru(COD)Cl (73 mg, 0.18 mmol). The resulting mixture was stirred for 1 h at 60 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:2 ethyl acetate/petroleum ether) to afford tert-butyl 6-(2-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a brown solid (962 mg, 22%). LCMS (ES, m/z): 403, 405 $[M+H]^+$.

[0165] The Intermediates in Table 10 were synthesized according to the procedure described for Intermediate 24-1 above.

Table 10.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
24-2	 tert-butyl 6-(3-hydroxybenzoyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	341
24-3	 tert-butyl 6-(3-bromo-4-methylbenzoyl)-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	417, 419
24-4	 tert-butyl 6-benzoyl-1,3-dihydro-2H-pyrrolo[3,4-c]pyridine-2-carboxylate	325

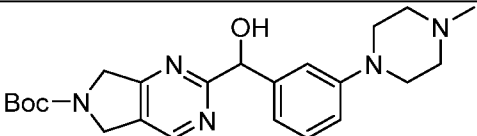
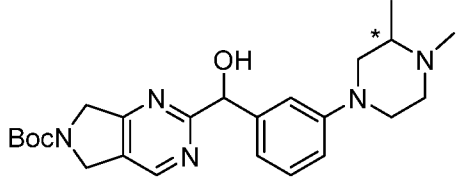
Intermediate 25-1. Tert-butyl 6-[hydroxy[2-(4-methylpiperazin-1-yl)phenyl]methyl]-1H, 2H, 3H-pyrrolo [3,4-c] pyridine-2-carboxylate



[0166] To a solution of tert-butyl 6-[2-(4-methylpiperazin-1-yl)benzoyl]-1H, 2H, 3H-pyrrolo [3,4-c] pyridine-2-carboxylate (200 mg, 0.43 mmol) in MeOH (10 mL) was added sodium borohydride (8 mg, 0.21 mmol). The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:10 MeOH/DCM) to afford tert-butyl 6-[hydroxy[2-(4-methylpiperazin-1-yl)phenyl]methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as yellow oil (170 mg, 85%). LCMS (ES, m/z): 425 [M+H]⁺.

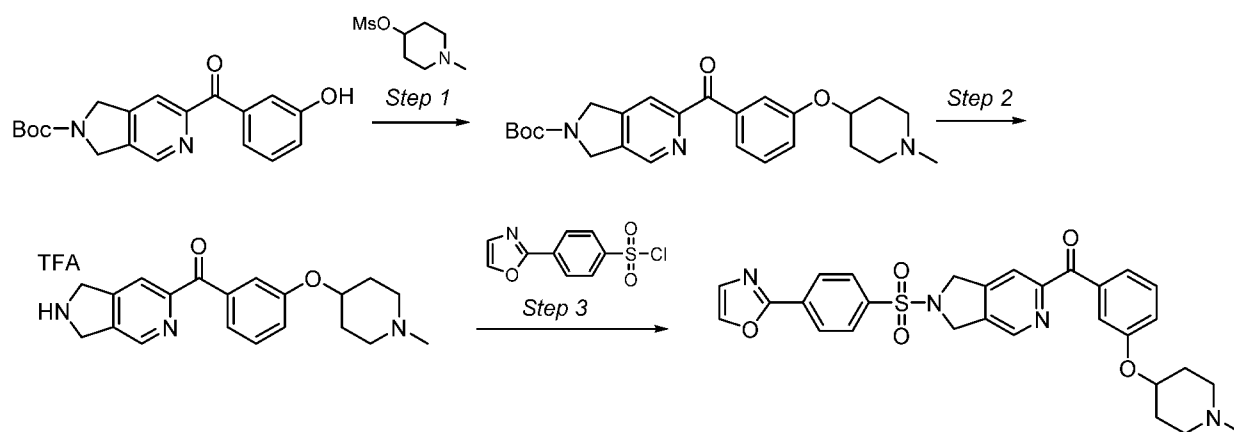
[0167] The Intermediates in Table 11 were synthesized according to the procedure described for Intermediate 25-1 above.

Table 11.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
25-2	 tert-butyl 2-(hydroxy(3-(4-methylpiperazin-1-yl)phenyl)methyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	426
25-3	 tert-butyl 2-((3-(3,4-dimethylpiperazin-1-yl)phenyl)(hydroxy)methyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	440

*Absolute stereochemistry not determined.

Intermediate 26-1. 1-methyl-4-(3-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine -6-carbonyl} phenoxy)piperidine



Step 1. Tert-butyl 6-{3-[(1-methylpiperidin-4-yl)oxy]benzoyl}-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0168] To a solution of tert-butyl 6-(3-hydroxybenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (500 mg, 1.47 mmol) in DMF (10 mL), was added 1-methylpiperidin-4-yl methanesulfonate (1.42 g, 7.34 mmol), cesium carbonate (1.44 g, 4.40 mmol) and potassium iodide (24 mg, 0.15 mmol). The resulting mixture was stirred for 16 h at 100 °C. After cooling to room temperature, the reaction mixture was poured into water (30 mL) and then extracted with ethyl acetate (3 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography

(eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 6-[3-[(1-methylpiperidin-4-yl)oxy]benzoyl]-1H,2H,3H-pyrrolo [3,4-c]pyridine-2-carboxylate as light yellow oil (400 mg, 62%). LCMS (ES, m/z): 438 [M+H]⁺.

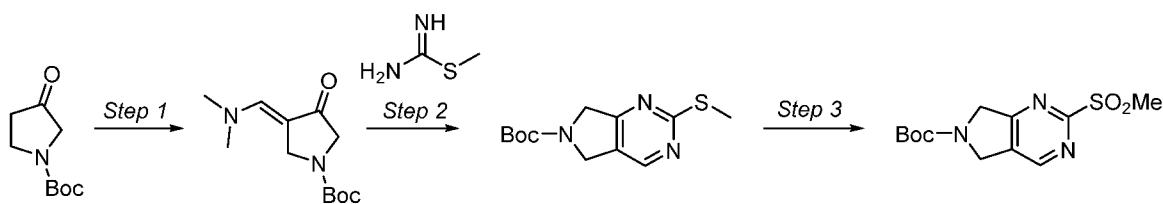
Step 2. 1-methyl-4-(3-{1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl}phenoxy)piperidine (TFA salt)

[0169] To a solution of tert-butyl 6-[3-[(1-methylpiperidin-4-yl)oxy]benzoyl]-1H,2H,3H-pyrrolo [3,4-c]pyridine -2-carboxylate (300 mg, 0.68 mmol) in dichloromethane (4 mL), was added trifluoroacetic acid (1 mL). The resulting solution was stirred for 2 h at 25 °C. The reaction mixture was concentrated under vacuum to afford 1-methyl-4-(3-[1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]phenoxy)piperidine (TFA salt) as light yellow oil (200 mg, 86%). LCMS (ES, m/z): 338 [M+H]⁺.

Step 3. 1-methyl-4-(3-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine -6-carbonyl} phenoxy)piperidine

[0170] To a solution of 1-methyl-4-(3-[1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]phenoxy)piperidine (TFA salt) (200 mg, 0.59 mmol) in DCM (8 mL) was added TEA (0.49 mL, 3.55 mmol) and 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride (144 mg, 0.59 mmol). The resulting mixture was stirred for 2 h at 25 °C and then concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 100: 0 to 90:10 dichloromethane/methanol) to afford 1-methyl-4-(3-[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo [3,4-c]pyridine-6-carbonyl] phenoxy)piperidine as light yellow oil (100 mg, 31%). LCMS (ES, m/z): 545 [M+H]⁺.

Intermediate 27-1. Tert-butyl 2-(3-bromobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



Step 1. Tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopyrrolidine-1-carboxylate

[0171] To tert-butyl 3-oxopyrrolidine-1-carboxylate (20 g, 102 mmol) was added dimethylformamide dimethyl acetal (200 mL). The resulting solution was stirred for 12 h at 140 °C. After cooling to room temperature, the resulting mixture was concentrated. The residue was dissolved with a minimum amount of DCM and then treated with hexane (100 mL). The resulting solids were

collected by filtration and dried under vacuum to afford tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopyrrolidine-1-carboxylate as a yellow solid (15 g, 58%). LCMS (ES, m/z): 241 [M+H]⁺.

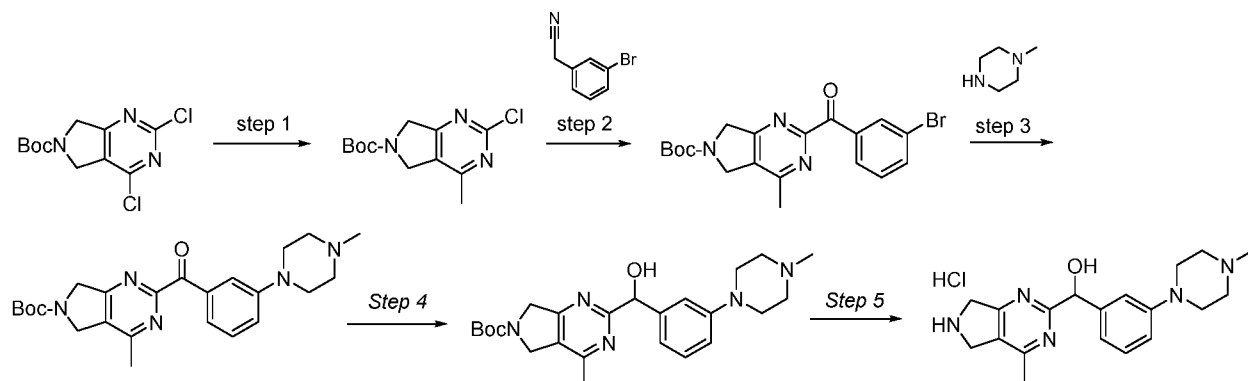
Step 2. Tert-butyl 2-(methylsulfanyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0172] To a solution of (methylsulfanyl)methanimidamide (17 g, 183 mmol) in EtOH (200 mL) was added sodium ethoxide (13 g, 183 mmol) at 0 °C. After stirring for 10 min, to the above solution was added tert-butyl (3E)-3-[(dimethylamino)methylidene]-4-oxopyrrolidine-1-carboxylate (15 g, 61.2 mmol). The resulting mixture was stirred for 4 h at 80 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The residue was dissolved with water (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:2 ethyl acetate/petroleum ether) to afford tert-butyl 2-(methylsulfanyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (4 g, 41%). LCMS (ES, m/z): 268 [M+H]⁺.

Step 3. Tert-butyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0173] To a solution of tert-butyl 2-(methylsulfanyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (4 g, 14.1 mmol) in DCM (80 mL) was added m-CPBA (7.5 g, 42.6 mmol). The resulting mixture was stirred for 5 h at 0 °C. The resulting mixture was washed with saturated sodium bicarbonate solution (5 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude product was purified by silica gel chromatography (eluting with 2:1 ethyl acetate/petroleum ether) to afford tert-butyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (4 g, 89%). LCMS (ES, m/z): 300 [M+H]⁺.

Intermediate 28-1. {4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)



Step 1. Tert-butyl 2-chloro-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0174] To a solution of tert-butyl 2,4-dichloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (1.10 g, 3.79 mmol) in tetrahydrofuran (20 mL) was added ferric acetylacetonate (416 mg, 1.18 mmol), and methylmagnesium chloride (2 mL, 3 M in THF) at 0 °C. The resulting mixture was stirred for 18 h at 0 °C. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:70 ethyl acetate/petroleum ether) to afford tert-butyl 2-chloro-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (550 mg, 48%). LCMS (ES, m/z): 270, 272 [$M+H$]⁺.

Step 2. Tert-butyl 2-(3-bromobenzoyl)-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0175] To a solution of 2-(3-bromophenyl)acetonitrile (600 mg, 3.06 mmol) in THF (10 mL), was added lithium bis(trimethylsilyl)amide (3 mL, 1 M in THF), and tert-butyl 2-chloro-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (550 mg, 2.04 mmol). The resulting mixture was stirred for 18 h at room temperature while oxygen was kept bubbling in. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 50:50 ethyl acetate/petroleum ether) to afford tert-butyl 2-(3-bromobenzoyl)-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a light yellow solid (380 mg, 40%). LCMS (ES, m/z): 418, 420 [$M+H$]⁺.

Step 3. Tert-butyl 4-methyl-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo [3,4-d]pyrimidine -6-carboxylate

[0176] To a solution of tert-butyl 2-(3-bromobenzoyl)-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (370 mg, 0.88 mmol) in 1,4-dioxane (10 mL) was added cesium carbonate

(865 mg, 2.66 mmol), 1-methylpiperazine (266 mg, 2.66 mmol), RuPhos (42 mg, 0.09 mmol), and RuPhos 3G (74 mg, 0.09 mmol). The resulting mixture was stirred for 18 h at 100 °C. After cooling to room temperature, the reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 80:20 ethyl acetate/petroleum ether) to afford tert-butyl 4-methyl-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (200 mg, 46%). LCMS (ES, m/z) 438 $[M+H]^+$.

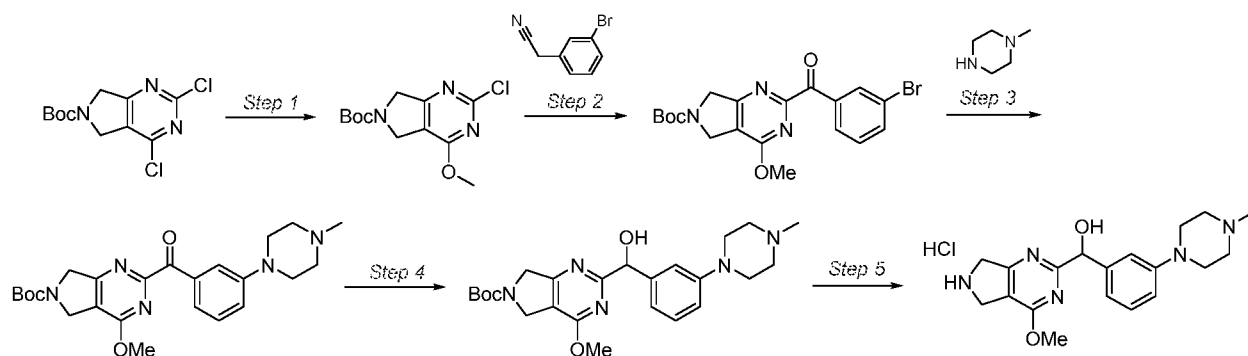
Step 4. Tert-butyl 2-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl}-4-methyl-5H,6H,7H-pyrrolo [3,4-d]pyrimidine-6-carboxylate

[0177] To a solution of tert-butyl 4-methyl-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo [3,4-d]pyrimidine -6-carboxylate (200 mg, 0.45 mmol) in methanol (5 mL), was added sodium borohydride (35 mg, 0.92 mmol). The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 1:10 methanol / dichloromethane) to afford tert-butyl 2-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl] -4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as yellow oil (180 mg, 80%). LCMS (ES, m/z): 440 $[M+H]^+$.

Step 5. {4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)

[0178] To a solution of tert-butyl 2-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl]-4-methyl-5H,6H,7H-pyrrolo [3,4-d]pyrimidine-6-carboxylate (180 mg, 0.41 mmol) in dichloromethane (3 mL) was added hydrochloric acid (3 mL, 4 N in 1,4-dioxane). The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under vacuum to afford [4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl] [3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) as a yellow solid (130 mg, 84%). LCMS (ES, m/z): 340 $[M+H]^+$.

Intermediate 29-1. {4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)



Step 1. Tert-butyl 2-chloro-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0179] To a solution of tert-butyl 2,4-dichloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (2.00 g, 6.55 mmol) in methanol (15 mL) was added a solution of sodium methoxide (447 mg, 7.86 mmol) in MeOH (5 mL) dropwise with stirring at 0 °C. The resulting mixture was stirred for 14 h at room temperature. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 40:60 ethyl acetate/petroleum ether) to afford tert-butyl 2-chloro-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as yellow oil (1.8 g, 82%). LCMS (ES, m/z): 286, 288 [M+H]⁺.

Step 2. Tert-butyl 2-(3-bromobenzoyl)-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0180] To a solution of tert-butyl 2-chloro-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (1.60 g, 5.60 mmol) in THF (20 mL) was added 2-(3-bromophenyl)acetonitrile (1.65 g, 8.40 mmol), and lithium hexamethyldisilazide solution (11.2 mL, 1.0 M in THF). The resulting mixture was stirred for 14 h at room temperature while oxygen was kept bubbling in. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 40:60 ethyl acetate/petroleum ether) to afford tert-butyl 2-(3-bromobenzoyl)-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (1.2 g, 49%). LCMS (ES, m/z): 434, 436 [M+H]⁺.

Step 3. Tert-butyl 4-methoxy-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0181] To a solution of tert-butyl 2-(3-bromobenzoyl)-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (500 mg, 1.15 mmol) in 1,4-dioxane (5 mL) was added 1-

methylpiperazine (0.79 mL, 11.5 mmol), cesium carbonate (1.13 g, 3.45 mmol), RuPhos (54 mg, 0.12 mmol), and RuPhos 3G (96 mg, 0.12 mmol). The resulting mixture was stirred for 3 h at 100 °C. After cooling to room temperature, the reaction mixture was poured into water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 100:1 to 10:1 dichloromethane/methanol) to afford tert-butyl 4-methoxy-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as yellow oil (350 mg, 57%). LCMS (ES, m/z): 454 [M+H]⁺.

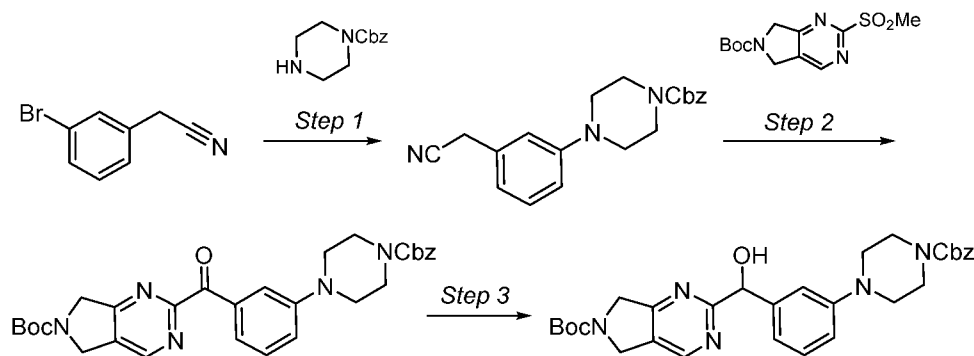
Step 4. Tert-butyl 2-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl}-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0182] To a solution of tert-butyl 4-methoxy-2-[3-(4-methylpiperazin-1-yl)benzoyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (350 mg, 0.77 mmol) in methanol (5 mL) was added sodium borohydride (44 mg, 1.16 mmol) at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated and diluted with water (2 mL). The reaction mixture was extracted with ethyl acetate (4 x 5 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 15:1 dichloromethane/methanol) to afford tert-butyl 2-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl}-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as yellow oil (200 mg, 57%). LCMS (ES, m/z): 456 [M+H]⁺.

Step 5. {4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)

[0183] To a solution of tert-butyl 2-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl}-4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (200 mg, 0.44 mmol) in dichloromethane (4 mL) was added hydrochloric acid (1 mL, 4 N in 1,4-dioxane). The resulting solution was stirred for 2 h at room temperature and concentrated under vacuum to afford {4-methoxy-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) as a yellow solid (60 mg, crude). LCMS (ES, m/z): 356 [M+H]⁺.

Intermediate 30-1. Benzyl 4-[3-({6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl} (hydroxy)methyl)phenyl]piperazine-1-carboxylate



Step 1. Benzyl 4-[3-(cyanomethyl)phenyl]piperazine-1-carboxylate

[0184] To a solution of 2-(3-bromophenyl)acetonitrile (3 g, 15.3 mmol) in 1,4-dioxane (50 mL), was added benzyl piperazine-1-carboxylate (6.74 g, 30.6 mmol), RuPhos (714 mg, 1.53 mmol), potassium phosphate (9.74 g, 45.9 mmol) and RuPhos 3G (1.28 g, 1.53 mmol). The resulting mixture was stirred for 16 h at 85 °C. After cooling to room temperature, the reaction mixture was poured into water (100 mL) and then extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford benzyl 4-[3-(cyanomethyl)phenyl]piperazine-1-carboxylate as a light yellow oil (1.0 g, 19.5%). LCMS (ES, m/z): 336 [M+H]⁺.

Step 2. Benzyl 4-(3-{6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonyl}phenyl)piperazine-1-carboxylate

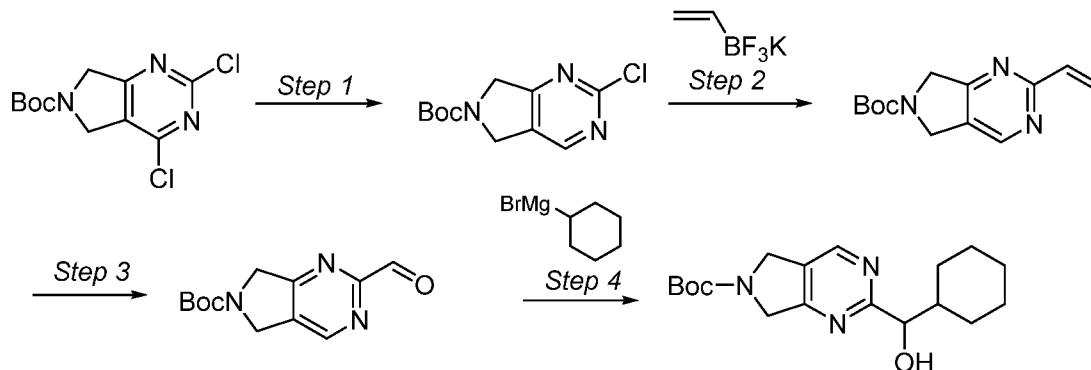
[0185] To a solution of benzyl 4-[3-(cyanomethyl)phenyl]piperazine-1-carboxylate (600 mg, 1.78 mmol) in THF (30 mL) was added tert-butyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (642 mg, 2.15 mmol) and potassium hexamethyldisilazide (3.58 mL, 1 M in THF). The resulting mixture was stirred for 4 h at 25 °C while oxygen was kept bubbling in. The reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford benzyl 4-(3-{6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}phenyl)piperazine-1-carboxylate as light yellow oil (350 mg, 48%). LCMS (ES, m/z): 544 [M+H]⁺.

Step 3. Benzyl 4-[3-({6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}(hydroxy)methyl)phenyl]piperazine-1-carboxylate

[0186] To a solution of benzyl 4-(3-{6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}phenyl)piperazine-1-carboxylate (390 mg, 0.72 mmol) in MeOH (10 mL) was added sodium borohydride (8 mg, 0.21 mmol). The resulting mixture was stirred for 2 h at 25 °C. The reaction was quenched by addition of water (0.5 mL). The resulting mixture was concentrated

under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford benzyl 4-[3-({6-[(tert-butoxy)carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}(hydroxy)methyl)phenyl]piperazine-1-carboxylate as light yellow oil (290 mg, 74%). LCMS (ES, m/z): 546 $[M+H]^+$.

Intermediate 31-1. Tert-butyl 2-[cyclohexyl(hydroxy)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



Step 1. Tert-butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0187] To a solution of tert-butyl 2,4-dichloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (3.0 g, 10.1 mmol) in MeOH (24 mL) was added zinc powder (1.3 g, 17.9 mmol) and acetic acid (5.8 mL, 101 mmol). The resulting mixture was stirred for 16 h at 50 °C. After cooling to room temperature, the reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:8 EA/PE) to afford tert-butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a white solid (1.5 g, 52%). LCMS (ES, m/z): 256, 258 $[M+H]^+$.

Step 2. Tert-butyl 2-ethenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0188] To a solution of tert-butyl 2-chloro-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (690 mg, 2.70 mmol) in 1,4-dioxane (20 mL) and water (4 mL) was added sodium carbonate (572 mg, 5.40 mmol), ethenyltrifluoro- λ^4 -borane potassium (542 mg, 4.05 mmol) and Pd(dppf)Cl₂ (197 mg, 0.27 mmol). The resulting mixture was stirred for 16 h at 100 °C. After cooling to room temperature, the reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 2-ethenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a light yellow solid (430 mg, 64%). LCMS (ES, m/z): 248 $[M+H]^+$.

Step 3. Tert-butyl 2-formyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

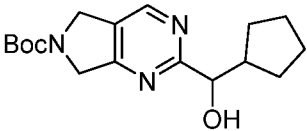
[0189] To a solution of tert-butyl 2-ethenyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (450 mg, 1.73 mmol) in THF (10 mL) and water (5 mL) was added sodium periodate (739 mg, 3.45 mmol) and osmium tetroxide (44 mg, 0.17 mmol). The resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was poured into water (15 mL) and then extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 2-formyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a light yellow solid (300 mg, 70%). LCMS (ES, m/z): 250 [M+H]⁺.

Step 4. Tert-butyl 2-[cyclohexyl(hydroxy)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

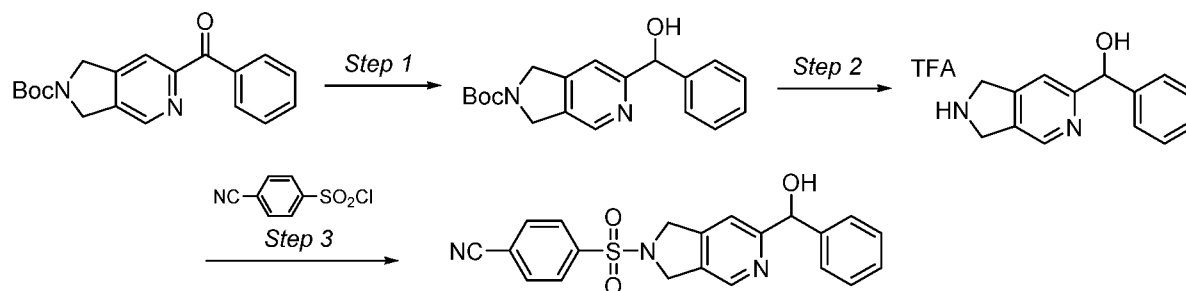
[0190] To a solution of tert-butyl 2-formyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (150 mg, 0.57 mmol) in THF (8 mL), was added bromo(cyclohexyl)magnesium (0.9 mL, 1.0 M in THF) at 0 °C. The resulting solution was stirred for 2 h at 25 °C. The reaction mixture was poured into saturated ammonium chloride (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 2-[cyclohexyl(hydroxy)methyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a light yellow solid (30 mg, 16%). LCMS (ES, m/z): 334 [M+H]⁺.

[0191] The Intermediate in Table 12 were synthesized according to the procedure described for Intermediate 31-1 above.

Table 12.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
31-2	 tert-butyl 2-(cyclopentyl(hydroxy)methyl)-5,7-dihydro-6H-pyrrolo[3,4-d]pyrimidine-6-carboxylate	320

Intermediate 32-1. 4-({6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)benzonitrile



Step 1. Tert-butyl 6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0192] To a solution of tert-butyl 6-benzoyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (340 mg, 1.05 mmol) in MeOH (10 mL), was added sodium borohydride (12 mg, 0.32 mmol). The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was poured into water (15 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (300 mg, 88%). LCMS (ES, m/z): 327 [M+H]⁺.

Step 2. Phenyl({1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (TFA salt)

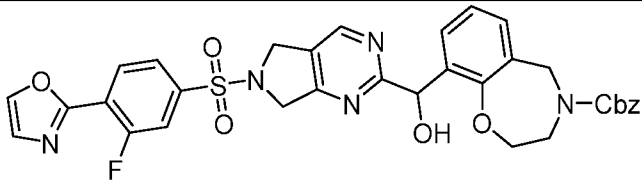
[0193] To a solution of tert-butyl 6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (280 mg, 0.86 mmol) in dichloromethane (4 mL) was added TFA (1 mL). The resulting mixture was stirred for 1 h at 25 °C. The reaction mixture was concentrated under vacuum to afford phenyl({1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (TFA salt) as light yellow oil (200 mg, crude). LCMS (ES, m/z): 227 [M+H]⁺.

Step 3. 4-({6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)benzonitrile

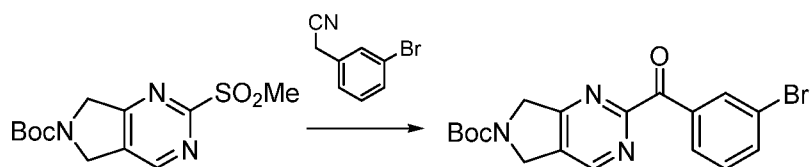
[0194] To a solution of phenyl({1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (TFA salt) (225 mg, 0.99 mmol) in dichloromethane (7 mL) was added TEA (0.55 mL, 3.98 mmol) and 4-cyanobenzene-1-sulfonyl chloride (200 mg, 0.99 mmol). The resulting mixture was stirred for 2 h at 25 °C and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford 4-({6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)benzonitrile as a white solid (200 mg, 51%). LCMS (ES, m/z): 392 [M+H]⁺.

[0195] The Intermediate in Table 13 were synthesized according to the procedure described for Intermediate 32-1 above.

Table 13.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
32-2	 benzyl 9-((6-((3-fluoro-4-(oxazol-2-yl)phenyl)sulfonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-2-yl)(hydroxy)methyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	658

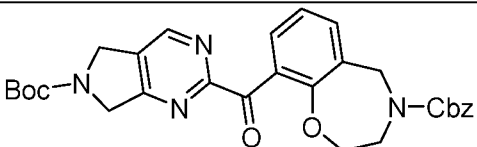
Intermediate 33-1. Tert-butyl 2-(3-bromobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



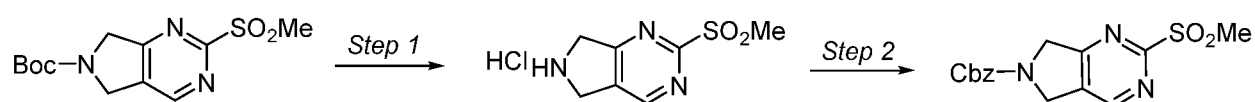
[0196] To a solution of 2-(3-bromophenyl)acetonitrile (1.96 g, 9.52 mmol) in THF (50 mL) was added tert-butyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (2 g, 6.35 mmol) and potassium bis(trimethylsilyl)amide solution (10 mL, 1 M in THF). The resulting mixture was stirred for 12 h at room temperature while oxygen was kept bubbling in. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:70 ethyl acetate/petroleum ether) to afford tert-butyl 2-(3-bromobenzoyl)-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (1.20 g, 44%). LCMS (ES, m/z): 404, 406 [M+H]⁺.

[0197] The Intermediate in Table 14 were synthesized according to the procedure described for Intermediate 33-1 above.

Table 14.

Intermediate	Compound	LCMS: (ESI) m/z [M+H] ⁺
33-2	 benzyl 9-(6-(tert-butoxycarbonyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine-2-carbonyl)-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate	531

Intermediate 34-1. Benzyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate



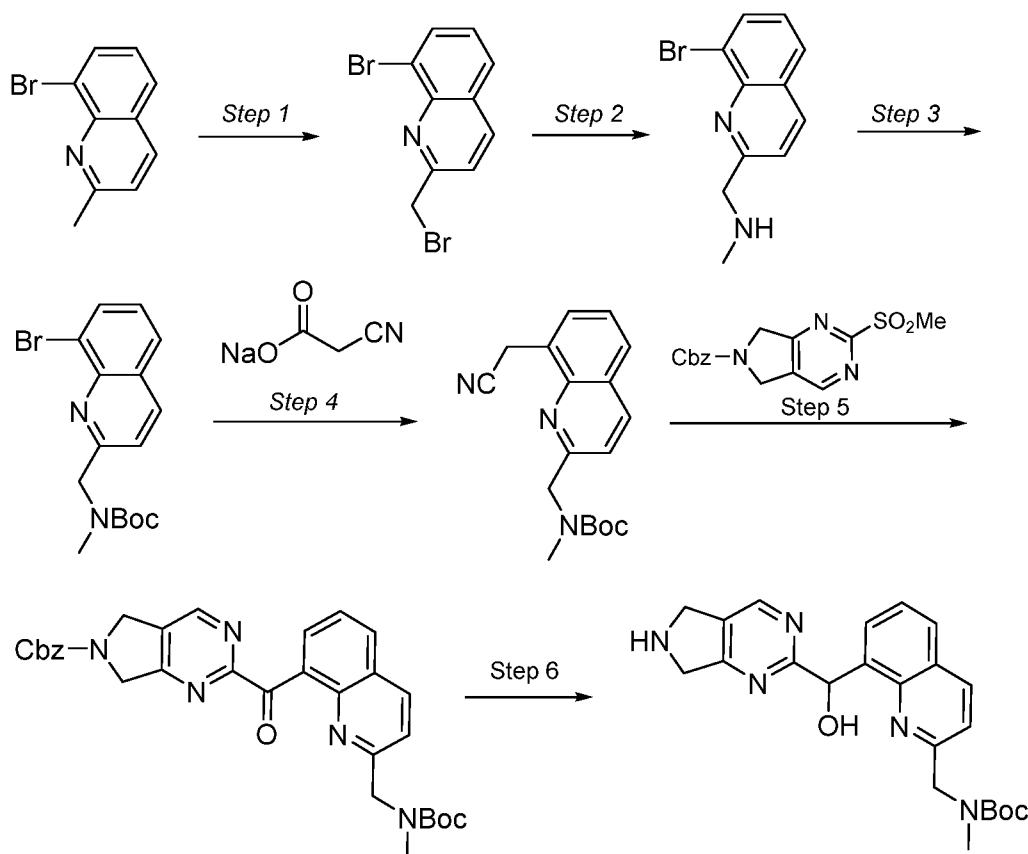
Step 1. 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine (HCl salt)

[0198] To tert-butyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (2 g, 6.35 mmol) was added hydrochloric acid (20 mL, 4 N in 1,4-dioxane). The resulting solution was stirred for 2 h at room temperature. The reaction mixture was concentrated to afford 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine HCl salt as yellow oil (1.4 g, crude). LCMS (ES, m/z): 200 [M+H]⁺.

Step 2. Benzyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0199] To a solution of 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine (HCl salt) (1.4 g, 6.33 mmol) in DCM (20 mL) was added TEA (2.77 mL, 19.0 mmol), and CbzCl (1.90 mL, 12.6 mmol) at 0 °C. The resulting solution was stirred for 5 h at room temperature. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 2:1 ethyl acetate/petroleum ether) to afford benzyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as a yellow solid (800 mg, 36%). LCMS (ES, m/z): 334 [M+H]⁺.

Intermediate 35-1. [(Tert-butoxy)(hydroxy)methyl](methyl)[(8-[5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonyl]quinolin-2-yl)methyl]amine



Step 1. 8-bromo-2-(bromomethyl)quinoline

[0200] To a solution of 8-bromo-2-methylquinoline (5 g, 21.4 mmol) in tetrachloride carbon (50 mL) was added NBS (4.4 g, 23.5 mmol) and AIBN (37 mg, 0.21 mmol). The resulting mixture was stirred overnight at 80 °C. After cooling to room temperature, the reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford 8-bromo-2-(bromomethyl)quinoline as a white solid (2 g, 28%). LCMS (ES, m/z): 300,302,304 $[M+H]^+$.

Step 2. [(8-bromoquinolin-2-yl)methyl](methyl)amine

[0201] To a solution of 8-bromo-2-(bromomethyl)quinoline (2 g, 5.32 mmol) in THF (20 mL) was added methylamine (20 mL, 2 M in THF). The resulting solution was stirred overnight at room temperature. The reaction mixture was filtered and concentrated under vacuum to afford [(8-bromoquinolin-2-yl)methyl](methyl)amine as yellow oil (800 mg, 48%). LCMS (ES, m/z): 251,253 $[M+H]^+$.

Step 3. Tert-butyl N-[(8-bromoquinolin-2-yl)methyl]-N-methylcarbamate

[0202] To a solution of [(8-bromoquinolin-2-yl)methyl](methyl)amine (800 mg, 2.55 mmol) in DCM (10 mL) was added Boc₂O (2.0 mL, 8.71 mmol). The resulting solution was stirred for 5 h at room temperature. The resulting mixture was concentrated. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 30:60 ethyl acetate/petroleum ether) to afford tert-butyl N-[(8-bromoquinolin-2-yl)methyl]-N-methylcarbamate as yellow oil (600 mg, 60%). LCMS (ES, m/z): 351,353 [M+H]⁺.

Step 4. Tert-butyl N-[[8-(cyanomethyl)quinolin-2-yl]methyl]-N-methylcarbamate

[0203] To a solution of tert-butyl N-[(8-bromoquinolin-2-yl)methyl]-N-methylcarbamate (600 mg, 1.54 mmol) in mesitylene (10 mL) was added Pd₂(allyl)₂Cl₂ (12 mg, 0.03 mmol), S-Phos (40 mg, 0.09 mmol), and sodium 2-cyanoacetate (260 mg, 2.31 mmol). The resulting mixture was stirred for 5 h at 140 °C. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-TLC (eluting with 1:2 ethyl acetate/petroleum ether) to afford tert-butyl N-[[8-(cyanomethyl)quinolin-2-yl]methyl]-N-methylcarbamate as yellow solid (500 mg, 94%). LCMS (ES, m/z): 312 [M+H]⁺.

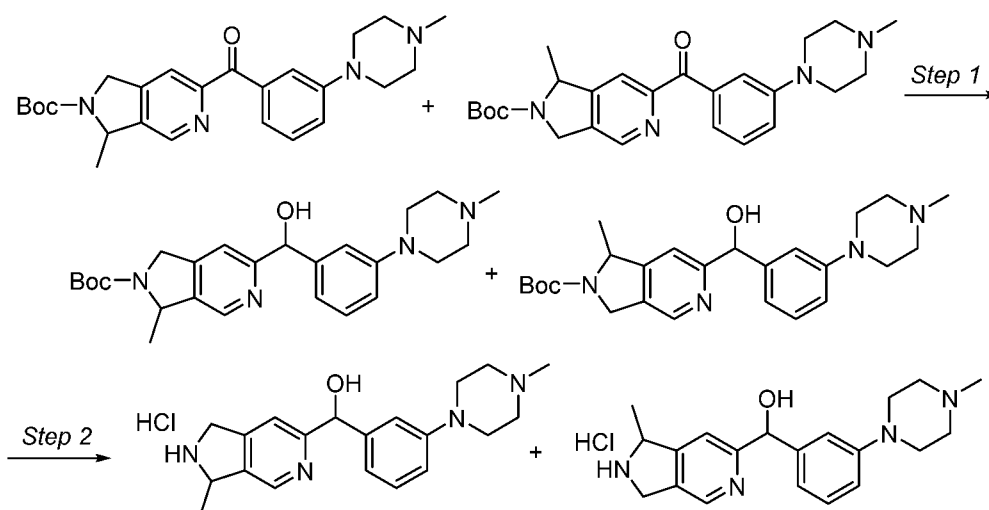
Step 5. Benzyl 2-[2-([[(tert-butoxy)carbonyl](methyl)amino)methyl]quinoline-8-carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate

[0204] To a solution of tert-butyl N-[[8-(cyanomethyl)quinolin-2-yl]methyl]-N-methylcarbamate (500 mg, 1.45 mmol) in THF (10 mL) was added benzyl 2-methanesulfonyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (535 mg, 1.45 mmol), and LiHMDS (2.2 mL, 1 M in THF). The resulting mixture was stirred for 2 days at room temperature while oxygen was kept bubbling in. The reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-TLC (eluting with 2:1 ethyl acetate/petroleum ether) to afford benzyl 2-[2-([[(tert-butoxy)carbonyl](methyl)amino)methyl]quinoline-8-carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate as yellow solid (150 mg, 18%). LCMS (ES, m/z): 554[M+H]⁺.

Step 6. [(Tert-butoxy)(hydroxy)methyl](methyl)[(8-[5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonyl]quinolin-2-yl)methyl]amine

[0205] To a solution of benzyl 2-[2-([(tert-butoxy)carbonyl](methyl)amino)methyl]quinoline-8-carbonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidine-6-carboxylate (150 mg, 0.26 mmol) in MeOH (5 mL) was added Pd/C (15 mg, 10% Pd). The resulting mixture was stirred for 24 h at room temperature under hydrogen atmosphere (2-3 atm). The reaction mixture was filtered and concentrated under vacuum to afford [(tert-butoxy)(hydroxy)methyl](methyl)[(8-[5H,6H,7H-pyrrolo[3,4-d]pyrimidine-2-carbonyl]quinolin-2-yl)methyl]amine as yellow oil (80 mg, 49%). LCMS (ES, m/z): 422 [M+H]⁺.

Intermediate 36-1. {3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) and {1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)



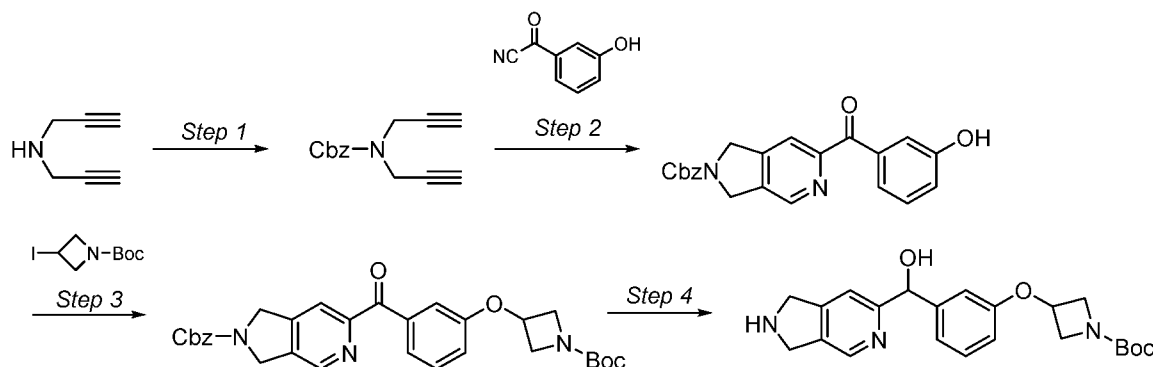
Step 1. Tert-butyl 6-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl}-3-methyl-1H,2H,3H-pyrrolo [3,4-c]pyridine-2-carboxylate and tert-butyl 6-{hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl} -1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0206] To a solution of tert-butyl 3-methyl-6-[3-(4-methylpiperazin-1-yl)benzoyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate and tert-butyl 1-methyl-6-[3-(4-methylpiperazin-1-yl)benzoyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (1 g, 2.29 mmol) in tert-butanol (8 mL) was added potassium tert-butoxide (12 mg, 0.11 mmol) and RuCl₂[(R)-DM-BINAP][(R)-DAIPEN] (27 mg, 0.02 mmol). The resulting mixture was stirred for 16 h at 25 °C under hydrogen atmosphere (8 atm). The reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 ethyl acetate/petroleum ether) to afford tert-butyl 6-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl]-3-methyl-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate and tert-butyl 6-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl]-1-methyl-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as light yellow oil (700 mg, 70%). LCMS (ES, m/z): 439 [M+H]⁺.

Step 2. **{3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) and {1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt)**

[0207] To a solution of tert-butyl 6-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl]-3-methyl-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate and tert-butyl 6-[hydroxy[3-(4-methylpiperazin-1-yl)phenyl]methyl]-1-methyl-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (600 mg, 1.36 mmol) in DCM (5 mL), was added hydrochloric acid (15 mL, 4 N in 1,4-dioxane). The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated under vacuum to afford {3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) and {1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol (HCl salt) as a light yellow solid (350 mg, 68%). LCMS (ES, m/z): 339 [M+H]⁺.

Intermediate 37-1. Tert-butyl 3-[3-[hydroxy([1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)]methyl]phenoxy]azetidine-1-carboxylate



Step 1. Benzyl N,N-bis(prop-2-yn-1-yl)carbamate

[0208] To a solution of bis(prop-2-yn-1-yl)amine (5 g, 51.0 mmol) in DCM (50 mL) was added TEA (21.7 mL, 153 mmol) and CbzCl (15.1 mL, 102 mmol). The resulting solution was stirred for 12 h at room temperature. The reaction mixture was poured into water (50 mL) and then extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford benzyl N,N-bis(prop-2-yn-1-yl)carbamate as yellow oil (8 g, 66%). LCMS (ES, m/z): 228 [M+H]⁺.

Step 2. Benzyl 6-(3-hydroxybenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0209] To a solution of 3-hydroxybenzoyl cyanide (1.6 g, 9.50 mmol) in DCE (20 mL) was added Cp*Ru(COD)Cl (61 mg, 0.16 mmol), and benzyl N,N-bis(prop-2-yn-1-yl)carbamate (2 g, 7.92 mmol) at 0 °C. The resulting solution was stirred for 1 h at 60 °C. After cooling to room temperature, the

reaction mixture was concentrated under vacuum. The resulting crude product was purified by Prep-TLC (eluting with 1:1 ethyl acetate / petroleum ether) to afford benzyl 6-(3-hydroxybenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (500 mg, 16%). LCMS (ES, m/z): 375 [M+H]⁺.

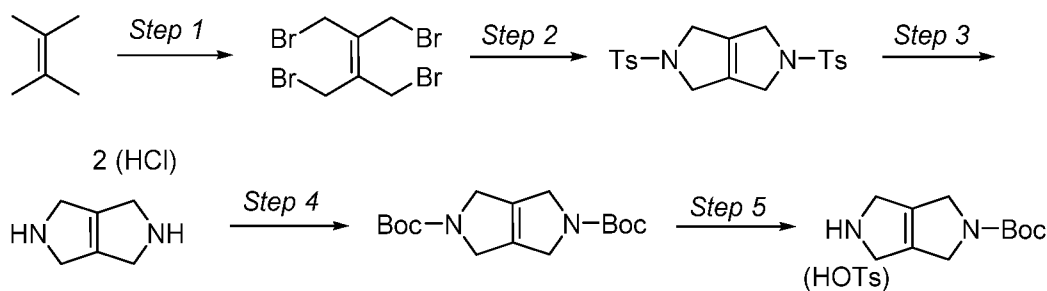
Step 3. Tert-butyl 3-(3-[2-[(benzyloxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]phenoxy)azetidine-1-carboxylate

[0210] To a solution of benzyl 6-(3-hydroxybenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (450 mg, 1.14 mmol) in DMF (5 mL) was added cesium carbonate (1.2 g, 3.43 mmol) and tert-butyl 3-iodoazetidine-1-carboxylate (1.0 g, 3.42 mmol). The resulting mixture was stirred for 5 h at 85 °C. After cooling to room temperature, the reaction mixture was poured into water (20 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-TLC (eluting with 1:1 ethyl acetate / petroleum ether) to afford benzyl N,N-bis(prop-2-yn-1-yl)carbamate as yellow oil (300 mg, 47%). LCMS (ES, m/z): 530 [M+H]⁺.

Step 4. Tert-butyl 3-[3-[hydroxy([1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenoxy]azetidine-1-carboxylate

[0211] To a solution of tert-butyl 3-(3-[2-[(benzyloxy)carbonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl]phenoxy) azetidine-1-carboxylate (250 mg, 0.45 mmol) in MeOH (10 mL) was added Pd/C (50 mg, 10% Pd). The resulting mixture was stirred for 5 h at room temperature under hydrogen atmosphere (2 -3 atm). The reaction mixture was filtered and concentrated under vacuum to afford tert-butyl 3-[3-[hydroxy([1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenoxy]azetidine-1-carboxylate as yellow oil (180 mg, 81%). LCMS (ES, m/z): 398 [M+H]⁺.

Intermediate 38-1. Tert-butyl 4,5-dihydropyrrolo[3,4-c]pyrrole-2(1H,3H,4H)-carboxylate (p-toluenesulfonate salt)



Step 1. 1,4-dibromo-2,3-bis(bromomethyl)but-2-ene

[0212] To a solution of 2,3-dimethylbut-2-ene (1000 g, 11.9 mol) in DCM (1000 mL) in 4 L 4-necked round bottom flask was added aqueous hydrobromide solution (150 mL, 48%). This was

followed by the slow addition of bromine (3.71 L, 62.0 mol) with stirring at 10-15 °C. The resulting mixture was stirred for 2 days at 45 °C in an oil bath. After cooling to room temperature, the reaction mixture was carefully poured into saturated sodium hydrogen sulfite solution (10 L). The precipitation was collected by filtration and dried in oven to afford 1,4-dibromo-2,3-bis(bromomethyl)but-2-ene as a light yellow solid (3000 g, 44%). GCMS: (EI, m/z): 398, 400, 402 [M]⁺.

Step 2. 2,5-ditosyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole

[0213] To a solution of 1,4-dibromo-2,3-bis(bromomethyl)but-2-ene (2000 g, 3.50 mol) in DMF (20 L) was added 4-methylbenzene-1-sulfonamide (2137 g, 12.5 mol) and potassium carbonate (5175 g, 37.4 mol). The resulting mixture was stirred for 2 days at room temperature. The reaction mixture was then slowly poured into water/ice (20 L). The precipitation was collected by filtration, washed with ethanol and dried in oven to afford 2,5-ditosyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole as a light yellow solid (1345 g, 78%). LCMS (ES, m/z): 419 [M+H]⁺.

Step 3. 1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole hydrobromide salt

[0214] To a solution of 2,5-ditosyl-1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole (1345 g, 2.73 mol) in aqueous hydrobromide solution (4500 mL, 48%) in 10 L 4-necked round-bottom flask, was added phenol (1270 g, 13.5 mol). The resulting mixture was stirred for 2 days at 120 °C. After cooling to room temperature, the aqueous layer was collected and concentrated under vacuum. The resulting solids were washed with DCM/MeOH (v:v = 10:1, 3 x 300 mL) and dried in oven to afford 1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole hydro bromide salt as a yellow solid (480 g, 61%). LCMS (ES, m/z): 111 [M+H]⁺.

Step 4. Di-tert-butyl pyrrolo[3,4-c]pyrrole-2,5(1H,3H,4H,6H)-dicarboxylate

[0215] To a suspension of 1,2,3,4,5,6-hexahydropyrrolo[3,4-c]pyrrole hydrobromide salt (458 g, 1.52 mol) in water (4 L) was added sodium bicarbonate (424 g, 5.05 mol). This was followed by the dropwise addition of a solution of di-tert-butyl dicarbonate (807 g, 3.70 mol) in methanol (500 mL) with stirring at 0 °C. The resulting solution was stirred for 16 h at 25 °C. The precipitation was collected by filtration and dried in oven to afford di-tert-butyl pyrrolo[3,4-c]pyrrole-2,5(1H,3H,4H,6H)-dicarboxylate as a white solid (300 g, 61%). LCMS (ES, m/z): 311[M+H]⁺.

Step 5. Tert-butyl 4,5-dihydropyrrolo[3,4-c]pyrrole-2(1H,3H,4H)-carboxylate (p-toluenesulfonate salt)

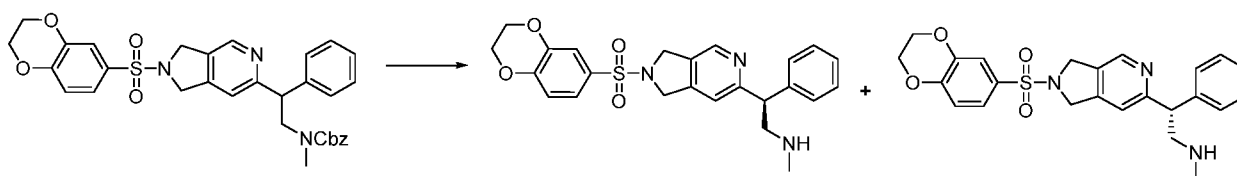
[0216] To a solution of di-tert-butyl pyrrolo[3,4-c]pyrrole-2,5(1H,3H,4H,6H)-dicarboxylate (200 g, 612 mmol) in propan-2-yl acetate (5 L) was added 4-methylbenzene-1-sulfonic acid (123 g, 647 mmol) in portions at 0 °C. The resulting mixture was stirred for 16 h at 55 °C in an oil bath. After

cooling to room temperature, the precipitation were collected by filtration and dried in oven to afford tert-butyl 4,5-dihydropyrrolo[3,4-c]pyrrole-2(1H,3H,4H)-carboxylate 4-methylbenzene-1-sulfonic acid salt as a yellow solid (197 g, 80%). LCMS (ES, m/z): 211[M+H]⁺.

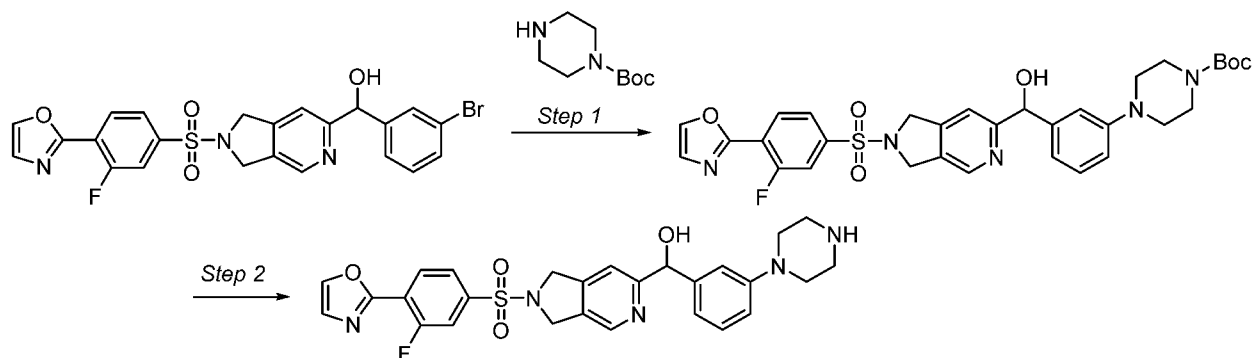
Example 2. Synthesis of Disclosed Compounds

Method A

[(2S)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl] (methyl)amine; [(2R)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl](methyl) amine



[0217] To a solution of (3-[2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl]phenyl)methyl N-methylcarbamate (100 mg, 0.17 mmol) in methanol (2 mL) was added palladium carbon (10 mg, 10 wt% palladium on charcoal). Then hydrogen was introduced with hydrogen balloon. The resulting mixture was stirred for 16 h at room temperature. The reaction mixture was filtered and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (5% to 30% over 25 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The two enantiomers were further separated by Chiral-Pre-HPLC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.1% DEA) and B: DCM (hold 50% B over 10 min); Detector: UV 254/220 nm; Retention time: 1st eluting isomer, 3.965 min; 2nd eluting isomer, 5.955 min). The product fractions of 1st eluting isomer were concentrated and lyophilized to afford a white solid (10.1 mg, 26%). ¹H-NMR (Methanol- d_4 , 400 MHz,) δ (ppm): 8.40 (s, 1H), 7.36-7.16 (m, 7H), 7.17 (s, 1H), 6.99-6.92 (m, 1H), 4.60 (s, 2H), 4.54 (s, 2H), 4.35-4.33 (m, 1H), 4.26-4.22 (m, 4H), 3.53-3.50 (m, 1H), 3.19-3.14 (m, 1H), 2.44 (s, 3H). LCMS (ES, m/z) 452 [M+H]⁺. The product fractions of 2nd eluting isomer were concentrated and lyophilized to a white solid (11.5 mg, 30%). ¹H-NMR (Methanol- d_4 , 400 MHz,) δ (ppm): 8.40 (s, 1H), 7.36-7.16 (m, 7H), 7.17 (s, 1H), 6.99-6.92 (m, 1H), 4.61 (s, 2H), 4.56 (s, 2H), 4.42-4.39 (m, 1H), 4.26-4.22 (m, 4H), 3.66-3.59 (m, 1H), 3.19-3.14 (m, 1H), 2.55 (s, 3H). LCMS (ES, m/z) 452 [M+H]⁺.

Method B**[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol****Step 1. Tert-butyl 4-[3-[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](hydroxy)methyl]phenyl]piperazine-1-carboxylate**

[0218] To a solution of (3-bromophenyl)([2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](hydroxy)methyl)phenyl]methanol (50 mg, 0.09 mmol) in 1,4-dioxane (2 mL) was added K_3PO_4 (61 mg, 0.29 mmol), tert-butyl piperazine-1-carboxylate (88 mg, 0.47 mmol), RuPhos 3G (16 mg, 0.02 mmol), and RuPhos (9 mg, 0.02 mmol). The resulting mixture was stirred for 2 h at 100 °C and then cooled to room temperature. The reaction mixture was poured into water (3 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 1:1 ethyl acetate/petroleum ether) to afford tert-butyl 4-[3-[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](hydroxy)methyl]phenyl]piperazine-1-carboxylate (40 mg, 67%). LCMS (ES, m/z) 636 $[M+H]^+$.

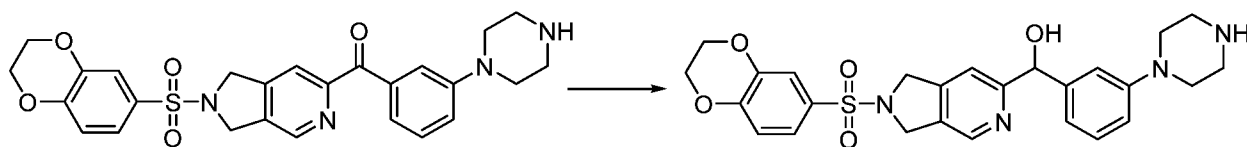
Step 2. [2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol

[0219] To a solution of tert-butyl 4-[3-[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](hydroxy)methyl]phenyl]piperazine-1-carboxylate (40 mg, 0.06 mmol) in dichloromethane (4 mL) was added TFA (1 mL). The resulting solution was stirred for 2 h at room temperature and concentrated under vacuum. The resulting mixture was basified to pH 8 with saturated potassium carbonate solution and then extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (25% to 45% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The product

fractions were concentrated and lyophilized to afford [2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol (13.1 mg, 37%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm) 8.35 (d, *J* = 16.8 Hz, 2H), 8.24-8.22 (m, 1H), 7.90-7.83 (m, 2H), 7.52 (s, 1H), 7.47 (s, 1H), 7.06-7.02 (m, 1H), 6.95 (s, 1H), 6.76-6.67 (m, 2H), 5.98 (d, *J* = 4.0 Hz, 1H), 5.60 (d, *J* = 4.0 Hz, 1H), 4.73-4.62 (m, 4H), 2.98-2.81 (m, 4H), 2.80-2.70 (m, 4H), 2.57-2.54 (m, 1H). LCMS (ES, *m/z*) 536 [M+H]⁺.

Method C

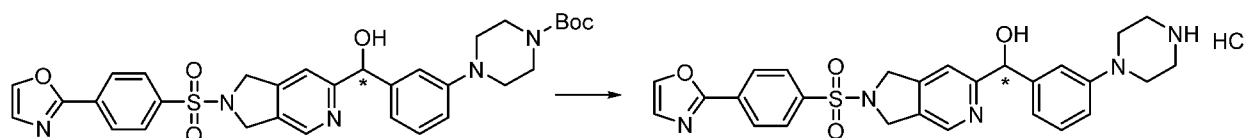
[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol



[0220] To a solution of 1-(3-[[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]carbonyl]phenyl)piperazine (30 mg, 0.05 mmol) in THF (0.5 mL) was added NaBH₄ (2 mg, 0.05 mmol) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. The reaction mixture was poured into water (3 mL) and then extracted with DCM (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 1:10 MeOH/DCM), and further purified by Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH₄HCO₃) and B: CH₃CN (20% to 42% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm). The product fractions were concentrated and lyophilized to afford [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol as a white solid (3.6 mg, 13%). ¹H-NMR (Methanol-*d*₄, 400 MHz) δ (ppm): 8.30 (s, 1H), 7.49 (s, 1H), 7.40-7.27 (m, 2H), 7.21-7.10 (m, 1H), 7.08-7.01 (m, 1H), 6.99-6.94 (m, 1H), 6.88-6.79 (m, 2H), 5.71 (s, 1H), 4.59 (s, 4H), 4.36-4.20 (m, 4H), 3.16-3.07 (m, 4H), 3.01-2.91 (m, 4H). LCMS (ES, *m/z*) 509 [M+H]⁺.

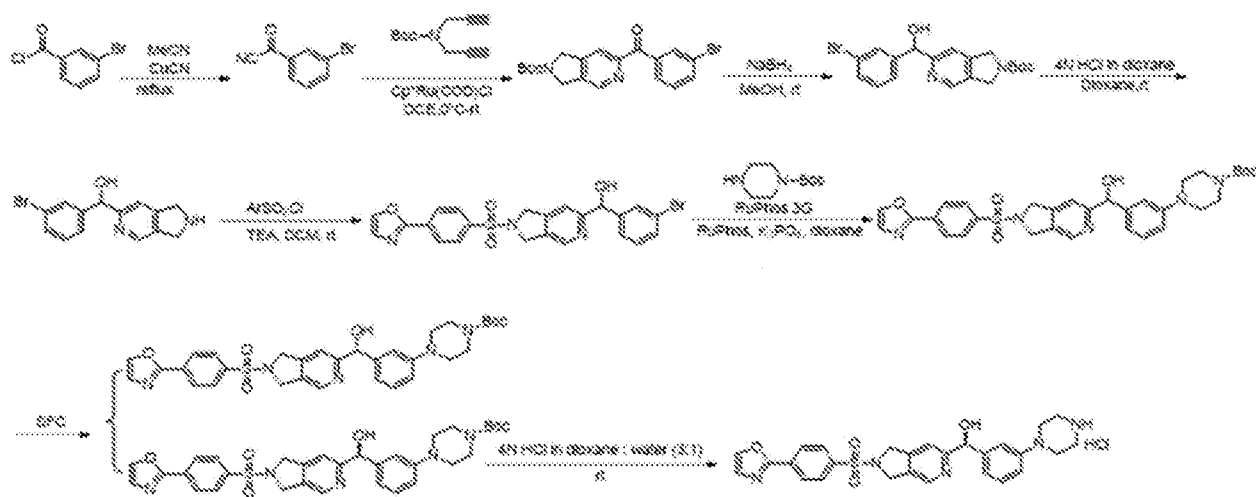
Method D-1

[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl] methanol (HCl salt)



[0221] To a solution of HCl in 1,4-dioxane (15 mL, 4 N) was added tert-butyl 4-[3-[(S)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methyl]phenyl]piperazine-1-carboxylate (1.30 g, 2.10 mmol) and water (5 mL). The resulting mixture was stirred for 4 h at room temperature. The reaction mixture was concentrated and lyophilized. The resulting crude product was purified by reverse phase chromatography (eluting with 10% to 50% MeCN/water). The product fractions were concentrated and lyophilized to afford (S)-[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl methanol hydrochloride salt as a white solid (857 mg, 79%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 9.09 (br s, 2H), 8.33 (d, *J* = 2.8 Hz, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 3.2 Hz, 2H), 7.12-7.08 (m, 1H), 7.03-7.01 (m, 1H), 6.80-6.77 (m, 2H), 6.07 (br s, 1H), 5.62 (s, 1H), 4.69-4.58 (m, 4H), 3.52-3.35 (m, 4H), 3.30-3.19 (m, 4H). LCMS (ES, *m/z*) 518 [M+H]⁺. *Absolute stereochemistry not determined.

Method D-2



Step 1. 3-bromobenzoyl cyanide

[0222] Into a 5-L 4-necked round-bottom flask, was placed 3-bromobenzoyl chloride (500 g, 2.27 mol, 1.00 equiv) and coppercyanide (612.1 g, 6.83 mol, 3.00 equiv) in acetonitrile (2.5 L). The resulting solution was stirred for 2 hours at 80°C and cooled to room temperature. Filtered and the filtrate was concentrated under vacuum. The resulting solution was extracted with 2x500 mL of ether and organic was concentrated under vacuum. The resulting solution was extracted with 3x500 mL of n-hexane, and organic was concentrated under vacuum. This resulted of 3-bromobenzoyl cyanide as a white solid (336 g, 71%).

Step 2. tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0223] Into a 3-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was added a solution of 3-bromobenzoyl cyanide (130 g, 0.62 mol, 1.00 equiv) in 1,2-dichloroethane (1.3 L). Then chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)ruthenium (II) (23.5g, 0.06 mol, 0.10 equiv) and tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (179.4 g, 0.93 mol, 1.50 equiv) was added at 0 °C. The resulting mixture was stirred for 4 h at room temperature. The resulting mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 20:80 ethyl acetate/petroleum ether) to afford tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (150 g, 60%).

Step 3. tert-butyl 6-[(3-bromophenyl) (hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0224] Into a 3-L 4-necked round-bottom flask, was placed tert-butyl 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (150 g, 370 mmol, 1.00 equiv) in methanol (1.5 L). Then, sodium borohydride (7.05 g, 180 mmol, 0.50 equiv) was added at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water (500 mL) and then extracted with ethyl acetate (3x1 L). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 40:60 ethyl acetate/petroleum ether) to afford tert-butyl 6-[(3-bromophenyl) (hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow solid (140 g, 93%).

Step 4. (3-bromophenyl)([1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol

[0225] Into a 2-L 3-necked round-bottom flask, was placed tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (120 g, 0.296 mol, 1.00 equiv) and 4N HCl (gas) in 1,4-dioxane (738.4 mL) in dioxane (1.2 L). The resulting solution was stirred for 4 hours at room temperature. The solids were collected by filtration. The filter cake was concentrated under vacuum. This resulted of (3-bromophenyl)([1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol as a green solid (96 g, crude).

Step 5. (3-bromophenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol

[0226] To a solution of 6-(3-bromobenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine HCl salt (100 g, 0.328 mol, 1.00 equiv) in DCM (1 L) was added triethylamine (99.8 g, 0.986 mol, 3.00equiv) at 0 °C. The resulting mixture was stirred for 30 min. Then a solution of 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride (79.9 g, 0.328 mol, 1.00 equiv) in DCM (500 mL) was added slowly. The resulting mixture was stirred for 2 hours at room temperature. The resulting mixture was concentrated under vacuum. The solids were washed with water and were an oven. This resulted in (3-bromophenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol as a yellow solid (129 g, 80% in two steps).

Step 6. tert-butyl 4-[3-[hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenyl]piperazine-1-carboxylate

[0227] Into a 3-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen was added a solution of (3-bromophenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (130 g, 0.253 mol, 1.00 equiv) in 1,4-dioxane (1.3 L) and maintained with an inert atmosphere of nitrogen 30 min. Then tert-butyl piperazine-1-carboxylate (141.2 g, 0.759 mol, 3.00 equiv), potassium phosphate (161.1 g, 0.759 mol, 3.00 equiv), RuPhos 3G (21.16 g, 25.3 mmol, 0.1 equiv) and RuPhos (11.8 g, 25.3 mmol, 0.1 equiv) was added. The resulting mixture was stirred for 16 h at 100 °C and cooled to room temperature. The reaction mixture was poured into water (500 mL) and then extracted with ethyl acetate (3x500 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 70:30 ethyl acetate/petroleum ether). This resulted in 80 g (51%) of tert-butyl 4-[3-[hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenyl]piperazine-1-carboxylate as a white solid (80 g, 51%).

Step 7. tert-butyl 4-[3-[(R)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenyl]piperazine-1-carboxylate and tert-butyl 4-[3-[(S)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methyl]phenyl]piperazine-1-carboxylate

[0228] The two enantiomers were separated by Prep-SFC (Column: CHIRALPAK,IF, 5 µm, 2 x 25 cm; Mobile Phase A: CO₂, Mobile Phase B: IPA:DCM = 1:1 (0.1%NH₃.H₂O) (keep 60% B over 12 min); Flow rate: 180 mL/min; Detector: 220 nm; Retention time, 7A: 6.1 min; 7B: 8.1 min). The

product fractions were concentrated and lyophilized to afford tert-butyl 4-[3-[(R)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)]methyl]phenyl]piperazine-1-carboxylate as a yellow solid (31 g, 38%) and tert-butyl 4-[3-[(S)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)]methyl]phenyl]piperazine-1-carboxylate (37 g, 46%) as a yellow solid.

Step 8. (S)-[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol hydrochloride salt

[0229] To a solution of tert-butyl 4-[3-[(S)-hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)]methyl]phenyl]piperazine-1-carboxylate (37 g, 59 mmol, 1.00 equiv) and water (148 mL) was added HCl in 1,4-dioxane (444 mL, 4 mol/L). The resulting mixture was stirred for 4 hours at room temperature. The reaction mixture was concentrated under vacuum. The resulting crude product was purified by reverse phase chromatography (eluting with 10% to 50% MeCN/water). The product fractions were concentrated and lyophilized to afford (S)-[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol hydrochloride salt as a white solid (16.7 g, 48%).

[0230] LCMS: (ES, m/z) 518 [M+H]⁺;

[0231] ¹H-NMR: (400 MHz, DMSO-d₆, ppm) δ 9.29 (br s, 2H), 8.33 (d, J = 2.8 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 3.2 Hz, 2H), 7.12-7.08 (m, 1H), 7.03-7.01 (m, 1H), 6.80-6.77 (m, 2H), 6.07 (br s, 1H), 5.62 (s, 1H), 4.69-4.58 (m, 4H), 3.52-3.35 (m, 4H), 3.30-3.19 (m, 4H).

Method D-3

[2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl] methanol (free base)

[0232] To a solution of tert-butyl 4-[3-[hydroxy([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)]methyl]phenyl]piperazine-1-carboxylate (300 mg, 0.49 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (1 mL). The resulting solution was stirred for 2 hours at room temperature and concentrated under vacuum to remove volatile components. The resulting aqueous mixture was brought to pH 8 with saturated potassium carbonate solution and then extracted with dichloromethane (2 x 5 mL). The combined organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified

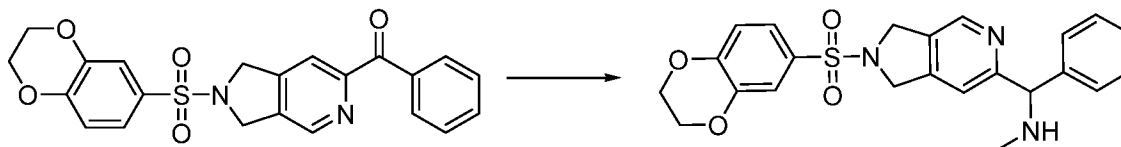
by silica gel chromatography (eluting with methanol/dichloromethane (1/9)) to afford the racemic product. The racemate was separated by Chiral Prep-HPLC with the following conditions: Column: Chiralpak IC-3 0.46 x 5 cm, 3 μ m; mobile phase A: MTBE (0.1% IPA), B: EtOH (50B over 6 min); Flow rate 1 mL/min, 220/254nm, Retention time: 0A, 2.35 min; 0B, 4.16 min). The product fractions were concentrated and lyophilized to afford (*R*)-(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(3-(piperazin-1-yl)phenyl)methanol (34.8 mg, 14%).

[0233] LCMS (ES, m/z) 518 $[M+H]^+$. $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.32 (d, $J=4.4$ Hz, 2H), 8.16 (d, $J=8.4$ Hz, 2H), 8.00 (d, $J=8.4$ Hz, 2H), 7.47 (s, 2 H), 7.05-7.01 (m, 1H), 6.95 (s, 1H), 6.71-6.66 (m, 2H), 5.97 (d, $J=3.2$ Hz, 1H), 5.59 (s, 1H), 4.69-4.58 (m, 4H), 2.98-2.96 (m, 4H), 2.85-2.78 (m 4H). And (*S*)-(2-((4-(oxazol-2-yl)phenyl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(3-(piperazin-1-yl)phenyl)methanol (34.1 mg, 13%). LCMS (ES, m/z) 518 $[M+H]^+$.

[0234] $^1\text{H-NMR}$ (DMSO- d_6 , 400 MHz) δ (ppm): 8.32 (d, $J=4.0$ Hz, 2H), 8.16 (d, $J=8.4$ Hz, 2H), 8.00 (d, $J=8.4$ Hz, 2H), 7.47 (s, 2 H), 7.05-7.01 (m, 1H), 6.94 (s, 1H), 6.71-6.66 (m, 2H), 5.97 (d, $J=3.2$ Hz, 1H), 5.59 (s, 1H), 4.65-4.59 (m, 4H), 2.96 (d, $J=4.8$ Hz, 4H), 2.85-2.79 (m 4H).

Method E

[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)methyl] (methyl)amine

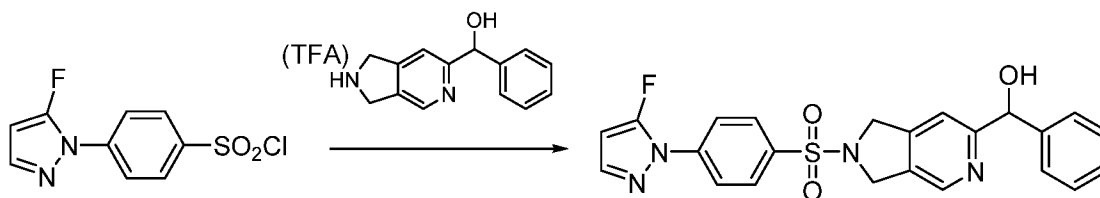


[0235] To a solution of 6-benzoyl-2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine (80 mg, 0.19 mmol) in methanol (1 mL) was added a solution of methylamine (0.5 mL, 2 M in THF). This was followed by the addition of titanium isopropoxide (108 mg, 0.38 mmol) with stirring at room temperature. The resulting solution was stirred for 16 h at room temperature. Then sodium borohydride (14 mg, 0.37 mmol) was added and the resulting mixture was stirred for an additional 2 h at room temperature. The reaction mixture was poured into water (2 mL) and then extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (30% to 65% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm). The product fractions were concentrated and lyophilized

to afford [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)methyl(methyl)amine as a white solid (37 mg, 45%). ¹H-NMR (Methanol-*d*₄, 400 MHz) δ (ppm): 8.37 (s, 1H), 7.40-7.18 (m, 8H), 7.00-6.93 (m, 1H), 4.79 (s, 1H), 4.62-4.53 (m, 4H), 4.31-4.21 (m, 4H), 2.31 (s, 3H). LCMS (ES, *m/z*) 438 [M+H]⁺.

Method F

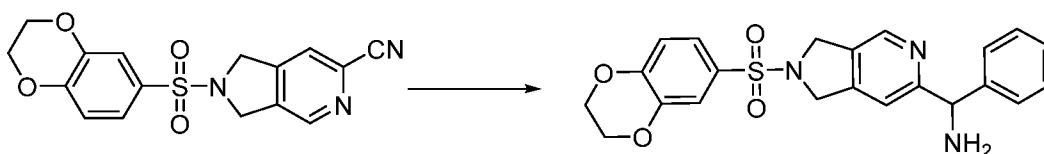
[2-[4-(5-fluoro-1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl](phenyl) methanol



[0236] To a solution of phenyl([1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl)methanol (TFA salt) (100 mg, 0.29 mmol) in dichloromethane (10 mL) and N,N-dimethylformamide (2 mL) was added potassium carbonate (122 mg, 0.88 mmol). The resulting mixture was stirred for 30 min at room temperature. To this was added 4-(5-fluoro-1H-pyrazol-1-yl) benzene-1-sulfonyl chloride (77 mg, 0.30 mmol). The resulting solution was stirred for 1 h at room temperature. The reaction mixture was poured into water (3 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by prep-TLC (eluting with 99:1 ethyl acetate/petroleum ether), and further purified by prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH₄HCO₃) and B: CH₃CN (30% B to 62% B over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The product fractions were concentrated and lyophilized to afford [2-[4-(5-fluoro-1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl](phenyl)methanol (13.6 mg, 10%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 8.33 (s, 1H), 8.07-7.98 (m, 2H), 7.88-7.85 (m, 2H), 7.74-7.73 (m, 1H), 7.49 (s, 1H), 7.31 (d, *J* = 6.8 Hz, 2H), 7.24-7.21 (m, 2H), 7.17-7.14 (m, 1H), 6.30-6.29 (m, 1H), 6.08-6.06 (m, 1H), 5.64 (d, *J* = 4.0 Hz, 1H), 4.69-4.57 (m, 4H). LCMS (ES, *m/z*) 451 [M+H]⁺.

Method G

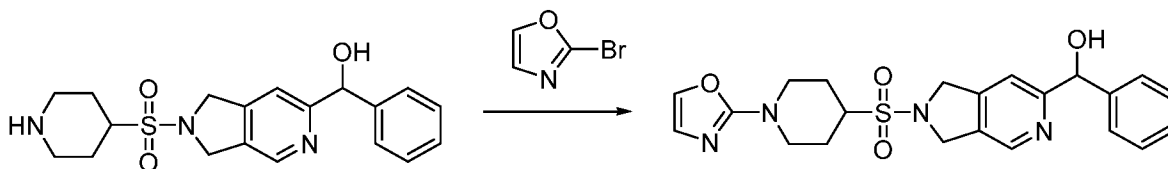
[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl](phenyl) methanamine



[0237] To a solution of 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonitrile (300 mg, 0.79 mmol) in toluene (10 mL) was added a solution of bromo(phenyl)magnesium (1.3 mL, 1M in tetrahydrofuran) dropwise with stirring at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction was quenched by addition of 2-methylpropan-1-ol (71 mg, 0.96 mmol). The resulting solution was stirred for 2 h at room temperature. This was followed by addition of NaBH₄ (100 mg, 2.64 mmol). The resulting solution was stirred for overnight at rt. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH₄HCO₃) and B: CH₃CN (30% to 58% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The product fractions were concentrated and lyophilized to afford [2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl](phenyl)methanamine as a white solid (250 mg 74%). ¹H-NMR (DMSO-*d*₆, 300 MHz) δ (ppm): 8.34 (s, 1H), 7.41 (s, 1H), 7.35-7.21 (m, 6H), 7.17-7.12 (m, 1H), 7.04-7.01 (m, 1H), 5.08 (s, 1H), 4.53 (s, 4H), 4.29-4.25 (m, 4H), 2.41 (s, 2H). LCMS (ES, *m/z*): 424 [M+H]⁺.

Method H

(2-[[1-(1,3-oxazol-2-yl)piperidin-4-yl]sulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl)(phenyl)methanol

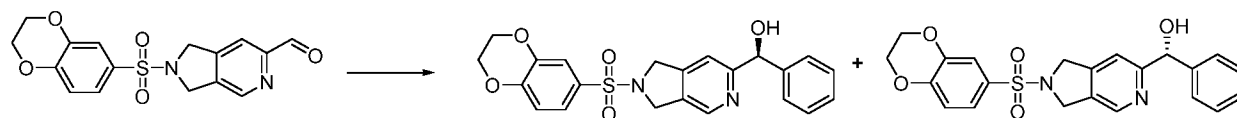


[0238] To a solution of phenyl[2-(piperidine-4-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl]methanol (80 mg, 0.21 mmol) in N,N-dimethylformamide (2 mL) was added DIEA (83 mg, 0.64 mmol). This was followed by the addition of 2-bromo-1,3-oxazole (64 mg, 0.43 mmol) at 70 °C with stirring. The resulting solution was stirred for 2 h at 70 °C and then cooled to room temperature. The reaction mixture was poured into water (5 mL) and then extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under

vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 methanol/dichloromethane), and further purified by Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (25% to 50% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm). The product fractions were concentrated and lyophilized to afford (2-[[1-(1,3-oxazol-2-yl)piperidin-4-yl]sulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanol as a white solid (13.0 mg, 14%). $^1\text{H-NMR}$ (Methanol- d_4 , 400 MHz) δ (ppm): 8.43 (s, 1H), 7.63 (s, 1H), 7.43-7.41 (m, 3H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 6.84 (s, 1H), 5.85 (s, 1H), 4.92-4.83 (s, 4H), 4.15-4.11 (m, 2H), 3.59-3.52 (m, 1H), 3.08-3.01 (m, 2H), 2.16-2.12 (m, 2H), 1.91-1.85 (m, 2H). LCMS (ES, m/z) 441 $[\text{M}+\text{H}]^+$.

Method I

(S)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)-methanol; (R)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)-methanol

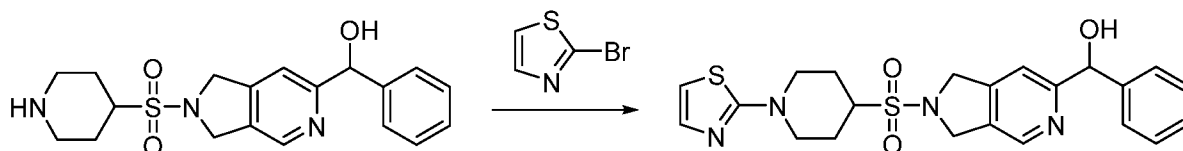


[0239] To a solution of 2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbaldehyde (40 mg, 0.10 mmol) in THF (1 mL) was added a solution of phenylmagnesium bromide (0.1 mL, 1.0 M in THF) dropwise with stirring at 0 °C. The resulting solution was stirred for 2 h at 0 °C. The reaction mixture was poured into saturated ammonium chloride solution (10 mL) and then extracted with EA (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (10% to 30% over 20 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The two enantiomers were further separated by Chiral Prep-HPLC (Column: CHIRALPAK IA, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol and B: DCM (hold 50% B over 25 min); Detector: UV 254/220 nm; Retention time: 1st eluting isomer, 7.62 min; 2nd eluting isomer, 9.89 min). The product fractions of 1st eluting isomer were concentrated and lyophilized to afford a white solid (2.1 mg, 5%). $^1\text{H-NMR}$ (Methanol- d_4 , 300 MHz) δ (ppm): 8.34-8.29 (m, 1H), 7.53-7.49 (m, 1H), 7.42-7.17 (m, 7H), 7.04-6.95 (m, 1H), 5.79 (s, 1H), 4.64 (s, 4H), 4.35-4.22 (m, 4H). LCMS (ES, m/z) 425 $[\text{M}+\text{H}]^+$. The product fractions of 2nd eluting isomer were concentrated and lyophilized to afford a white solid (1.4 mg, 3%). $^1\text{H-NMR}$ (Methanol- d_4 , 300 MHz)

δ (ppm): 8.34-8.29 (m, 1H), 7.53-7.49 (m, 1H), 7.42-7.17 (m, 7H), 7.04-6.95 (m, 1H), 5.79 (s, 1H), 4.64 (s, 4H), 4.35-4.22 (m, 4H). LCMS (ES, m/z) 425 $[M+H]^+$.

Method J

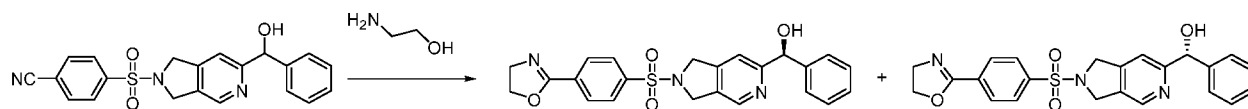
Phenyl(2-[[1-(1,3-thiazol-2-yl)piperidin-4-yl]sulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol



[0240] To a solution of phenyl[2-(piperidine-4-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol (40 mg, 0.11 mmol) in 1,4-dioxane (1 mL), was added 2-bromo-1,3-thiazole (18 mg, 0.11 mmol), Cs_2CO_3 (105 mg, 0.32 mmol) and RuPhos 3G (10 mg, 0.01 mmol). The resulting mixture was stirred for 16 h at 100 °C and then cooled to room temperature. The reaction mixture was poured into water (2 mL) and then extracted with ethyl acetate (2 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 0:100 to 10:90 methanol/dichloromethane) and further purified by Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μm , 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (30% to 65% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm). The product fractions were concentrated and lyophilized to afford phenyl(2-[[1-(1,3-thiazol-2-yl)piperidin-4-yl]sulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol as a white solid (2.0 mg, 4%). ^1H -NMR (CDCl_3 , 400 MHz,) δ (ppm): 8.51 (s, 1H), 7.47-7.35 (m, 4H), 7.32-7.31 (m, 1H), 7.19 (s, 1H), 7.10 (s, 1H), 6.62-6.60 (s, 1H), 5.79 (s, 1H), 4.98 (s, 1H), 4.87-4.83 (m, 2H), 4.79-4.69 (m, 2H), 4.19-4.16 (m, 2H), 3.29-3.22 (m, 1H), 3.07-3.01 (m, 2H), 2.23-2.20 (m, 2H), 2.06-1.96 (m, 2H). LCMS (ES, m/z) 457 $[M+H]^+$.

Method K

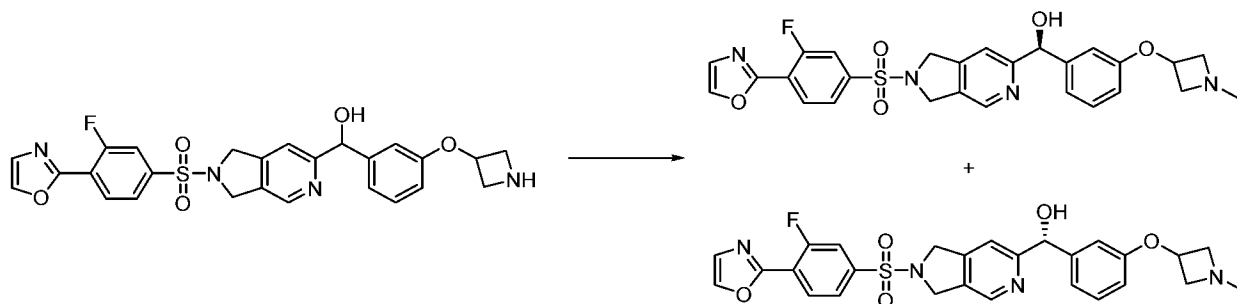
(S)-{2-[4-(4,5-dihydro-1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl) methanol; (R)-{2-[4-(4,5-dihydro-1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol



[0241] To a solution of 4-({6-[hydroxy(phenyl)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)benzonitrile (150 mg, 0.38 mmol) in 2-aminoethan-1-ol (1 mL), was added indium chloride (8 mg, 0.04 mmol). The resulting mixture was irradiated with microwave for 40 min at 80 °C. After cooling to room temperature, the reaction mixture was concentrated under vacuum. The resulting crude product was purified by silica gel chromatography (eluting with 100:0 to 80:20 dichloromethane/methanol). The product fractions were concentrated under vacuum. The two enantiomers were further separated by Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% DEA), B: EtOH; Gradient: keep 50% B over 24 min; Flow rate: 18 mL/min; Detector: UV 254/220 nm; Retention time: 1st eluting isomer, 12.618 min; 2nd eluting isomer, 19.401 min). The product fractions of the 1st eluting isomer were concentrated and lyophilized to afford a white solid (13.0 mg, 8%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 8.32 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.49 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25 (t, *J* = 8.0 Hz, 2H), 7.19-7.16 (m, 1H), 6.08 (d, *J* = 4.0 Hz, 1H), 5.67 (d, *J* = 4.0 Hz, 1H), 4.71-4.54 (m, 4H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.98 (t, *J* = 8.0 Hz, 2H). LCMS (ES, *m/z*): 436 [M+H]⁺. The product fractions of the 2nd eluting isomer were concentrated and lyophilized to afford a white solid (13.5 mg, 8%). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 8.32 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.49 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25 (t, *J* = 8.0 Hz, 2H), 7.19-7.16 (m, 1H), 6.08 (d, *J* = 4.0 Hz, 1H), 5.67 (d, *J* = 4.0 Hz, 1H), 4.71-4.54 (m, 4H), 4.43 (t, *J* = 8.0 Hz, 2H), 3.98 (t, *J* = 8.0 Hz, 2H). LCMS (ES, *m/z*): 436 [M+H]⁺.

Method L

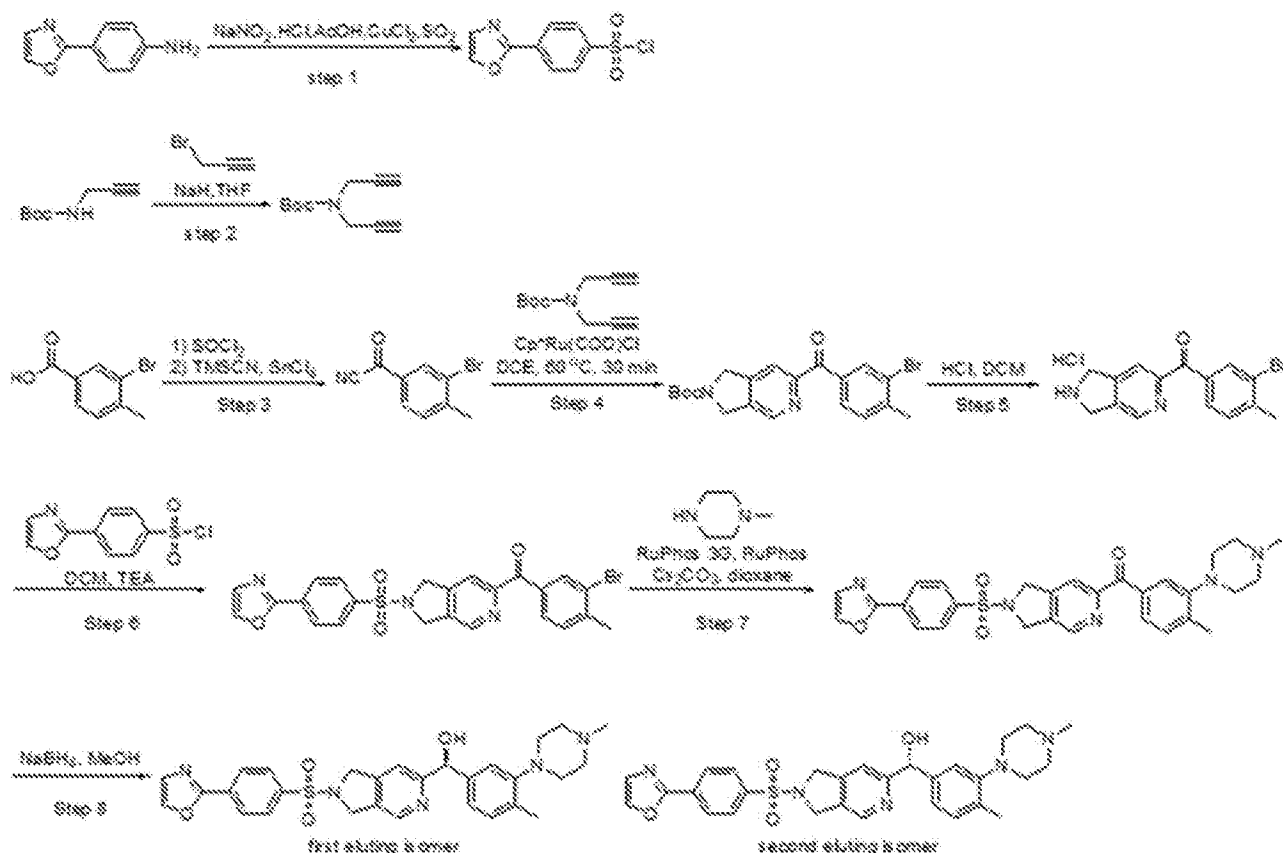
(S)-[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]([3-[(1-methylazetidin-3-yl)oxy]phenyl])methanol;
 (R)-[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]([3-[(1-methylazetidin-3-yl)oxy]phenyl])methanol



[0242] To a solution of [3-(azetidin-3-yloxy)phenyl]([2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (TFA salt) (80 mg, 0.14 mmol) in MeOH (2 mL) was added formaldehyde (1 mL, 30% in water). The resulting solution was stirred for 30 min at room temperature. This was followed by the addition of STAB (92 mg, 0.41 mmol). The resulting solution was stirred for 12 h at room temperature. The reaction mixture was poured into water (10 mL) and then extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The resulting crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH_4HCO_3) and B: CH_3CN (25% to 50% in 7 min); Flow rate: 60 mL/min; Detector: UV 220 nm). The product fractions were concentrated under vacuum. The two enantiomers were further separated by Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH (containing 0.1% DEA) and B: DCM (keep 40% B in 15 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1st eluting isomer, 10.772 min; 2nd eluting isomer, 13.314 min). The product fractions were concentrated and lyophilized to afford 1st eluting isomer as a white solid (12.4 mg, 16%). ¹H-NMR ($\text{DMSO}-d_6$, 400 MHz) δ (ppm): 8.38 (s, 1H), 8.34 (s, 1H), 8.24-8.20 (m, 1H), 7.90-7.83 (m, 2H), 7.53 (s, 1H), 7.47 (s, 1H), 7.14-7.10 (m, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.60-6.57 (m, 1H), 6.10 (d, J = 4.0 Hz, 1H), 5.63 (d, J = 4.4 Hz, 1H), 4.70-4.63 (m, 5H), 3.71-3.68 (m, 2H), 2.92-2.89 (m, 2H), 2.27 (s, 3H). LCMS (ES, m/z): 537 $[\text{M}+\text{H}]^+$. The product fractions were concentrated and lyophilized to afford 2nd eluting isomer as a white solid (13.3 mg, 18%). ¹H-NMR ($\text{DMSO}-d_6$, 400 MHz) δ (ppm): 8.38 (s, 1H), 8.34 (s, 1H), 8.24-8.20 (m, 1H), 7.90-7.83 (m, 2H), 7.53 (s, 1H), 7.47 (s, 1H), 7.14-7.10 (m, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.60-6.58 (m, 1H), 6.10 (d, J = 4.4 Hz, 1H), 5.63 (d, J = 4.0 Hz, 1H), 4.69-4.65 (m, 5H), 3.74-3.71 (m, 2H), 2.92-2.89 (m, 2H), 2.29 (s, 3H). LCMS (ES, m/z): 537 $[\text{M}+\text{H}]^+$.

Method M

(S)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl])methanol (first eluting isomer); (R)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl])methanol (second eluting isomer)



Step 1. 4-(1,3-oxazol-2-yl)benzenesulfonyl chloride

[0243] To a stirred mixture of 4-(1,3-oxazol-2-yl)aniline (1.00 g, 6.24 mmol) in conc. HCl (12 mL) and acetic acid (4 mL) was added NaNO₂ (517 mg, 7.49 mmol) in water (0.5 mL) dropwise at -10 °C. The mixture was stirred for 1 h at 0 °C to afford the fresh prepared diazonium salt (mixture A). In a separated 3-necked round-bottom flask, SO₂ was pumped into the stirred mixture of CuCl₂ (235 mg, 1.75 mmol) in acetic acid (20 mL) for 2 h at 20 °C to afford mixture B. The mixture A was then added into the mixture B at 20 °C. The resulting mixture was stirred for additional overnight at 25 °C. The reaction mixture was diluted with water (40 mL), the precipitated solids were collected by filtration, washed with water (2 x 20 mL) and dried under vacuum to afford 4-(1,3-oxazol-2-yl)benzenesulfonyl chloride (1.20 g, 67%) as an off-white solid. LCMS (ES, m/z): 244, 246 [M+H]⁺.

Step 2. tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate

[0244] To a stirred mixture of tert-butyl N-(prop-2-yn-1-yl)carbamate (5.00 g, 30.6 mmol) in DMF (50 mL) was added NaH (1.35 g, 33.7 mmol, 60%) in portions at 0 °C. The resulting mixture was stirred for 30 min at 0 °C under nitrogen atmosphere. This was followed by the additional of 3-bromoprop-1-yne (4.60 g, 36.7 mmol). The resulting mixture was stirred for 3 h at 26 °C under nitrogen atmosphere. The reaction mixture was poured into water/ice (100 mL) and extracted with

ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (2.60 g, 42%) as a yellow oil. LCMS (ES, m/z): 194 [M+H]⁺.

Step 3. 3-bromo-4-methylbenzoyl cyanide

[0245] A mixture of 3-bromo-4-methylbenzoic acid (80 g, 316 mmol, 85%) in SOCl₂ (70 mL) was stirred for 2 h at 80 °C. The mixture was cooled to room temperature and concentrated under vacuum. The fresh prepared acyl chloride was dissolved in DCM (900 mL), to the above mixture was added SnCl₄ (43.4 g, 158 mmol) and TMSCN (34.6 g, 332 mmol). The resulting mixture was stirred for 2 h at 25 °C. The reaction mixture was poured into water (200 mL) and extracted with DCM (3 x 500 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with ethyl acetate/petroleum ether (1/10)) to afford 3-bromo-4-methylbenzoyl cyanide as yellow oil (35.2 g, 49%). LCMS (ES, m/z): 224, 226 [M+H]⁺.

Step 4. Tert-butyl 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0246] To a solution of 3-bromo-4-methylbenzoyl cyanide (2.50 g, 0.01 mol) in DCE (250 mL) was added tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (1.21 g, 0.01 mol), chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)ruthenium(II) (0.35 g, 0.92 mmol). The resulting mixture was stirred for 1 h at 60 °C. The mixture was cooled to room temperature and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with ethyl acetate/petroleum ether (1/9)) to afford tert-butyl 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as yellow solid (2.50 g, 53%). LCMS (ES, m/z): 417, 419 [M+H]⁺.

Step 5. 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine hydrochloride

[0247] To a solution of tert-butyl 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.50 g, 6.01 mmol) in DCM (30 mL) was added HCl in dioxane (10 mL, 4 M). The resulting solution was stirred for 2 h at room temperature. The mixture was concentrated under vacuum to afford 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine hydrochloride as yellow solid (1.90 g, 90%). LCMS (ES, m/z): 317, 319 [M-HCl+H]⁺.

Step 6. 2-(4-{[6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-yl]sulfonyl}phenyl)-1,3-oxazole

[0248] To a mixture of 6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine hydrochloride (800 mg, 2.27 mmol) in DCM (30 mL) was added triethylamine (0.87 mL, 6.73 mmol) and 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride (660 mg, 2.71 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 25 °C. The mixture was concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with ethyl acetate/petroleum ether (1/10)) to afford 2-(4-{[6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-yl]sulfonyl}phenyl)-1,3-oxazole as a white solid (750 mg, 63%). LCMS (ES, m/z): 524,526 [M+H]⁺.

Step 7. 1-methyl-4-(2-methyl-5-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl}phenyl)piperazine

[0249] To a mixture of 2-(4-{[6-(3-bromo-4-methylbenzoyl)-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-yl]sulfonyl}phenyl)-1,3-oxazole (600 mg, 1.15 mmol) in 1,4-dioxane (70 mL) was added 1-methylpiperazine (1.20 g, 12.0 mmol), RuPhos-Pd 3G (100 mg, 0.12 mmol), RuPhos (600 mg, 1.28 mmol) and Cs₂CO₃ (1.10 g, 3.34 mmol). The resulting mixture was stirred for 5 h at 100 °C. The mixture was cooled to room temperature, poured into water (50 mL) and extracted with ethyl acetate (3 x 120 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with methanol/dichloromethane (1/10)) to afford 1-methyl-4-(2-methyl-5-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl}phenyl)piperazine as a white solid (400 mg, 64%). LCMS (ES, m/z): 544 [M+H]⁺.

Step 8. (S)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl})methanol (PH-FMA-PJ00135-640-0A, first eluting isomer) and (R)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl})methanol (PH-FMA-PJ00135-640-0B, second eluting isomer)

[0250] To a mixture of 1-methyl-4-(2-methyl-5-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-carbonyl}phenyl)piperazine (250 mg, 0.46 mmol) in methanol (3 mL) was added NaBH₄ (16 mg, 0.42 mmol) in portions at 0 °C. The resulting mixture was stirred for

1 h at 25 °C. The mixture was poured into water (25 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with methanol/dichloromethane (1/9)) to afford the racemic product. The racemate was separated by Chiral Prep-HPLC with the following conditions: Column: Chiralpak IC 2 x 25 cm, 5µm; mobile phase A: MTBE (0.2% IPA), B: MeOH (50B to 50B in 18 min); Flow rate 20 mL/min, 220/254nm, RT1: 15.54, RT2: 19.22. The product fractions were concentrated and lyophilized to afford (S)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl})methanol (first eluting isomer, RT1: 15.54) (34.4 mg, 15.97%) as a white solid. And (R)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-6-yl})methanol (second eluting isomer, RT2: 19.22) (32.6 mg, 15.13%) as a white solid.

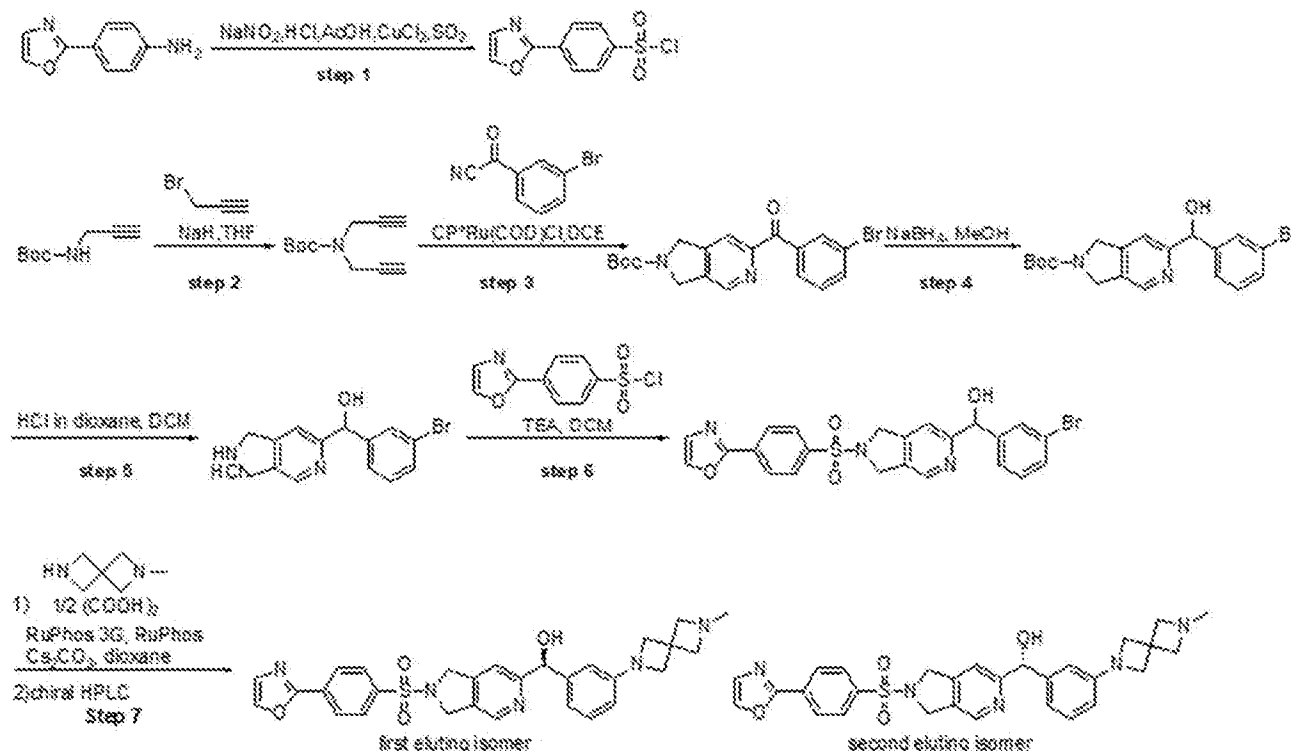
[0251] First eluting isomer: ¹H-NMR (DMSO, 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 5.99 (d, J = 4.0 Hz, 1H), 5.60 (d, J = 4.0 Hz, 1H), 4.65-4.59 (m, 4H), 2.76 (br s, 4H), 2.43 (br s, 4H), 2.21 (s, 3H), 2.13 (s, 3H). LCMS (ES, m/z): 546 [M+H]⁺.

[0252] Second eluting isomer: ¹H-NMR (DMSO, 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47-7.45 (m, 2H), 7.04 (s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.79-6.77 (m, 1H), 5.99 (d, J = 4.4 Hz, 1H), 5.60 (d, J = 4.0 Hz, 1H), 4.69-4.59 (m, 4H), 2.76 (br s, 4H), 2.45 (br s, 4H), 2.23 (s, 3H), 2.13 (s, 3H). LCMS (ES, m/z): 546 [M+H]⁺.

Method N

(S)-(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (first eluting isomer); (R)-

(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (second eluting isomer)



Step 1. 4-(1,3-oxazol-2-yl)benzenesulfonyl chloride

[0253] To a stirred mixture of 4-(1,3-oxazol-2-yl)aniline (1.00 g, 6.24 mmol) in conc. HCl (12 mL) and acetic acid (4 mL) was added NaNO_2 (517 mg, 7.49 mmol) in water (0.5 mL) dropwise at $-10\text{ }^\circ\text{C}$. The mixture was stirred for 1 h at $0\text{ }^\circ\text{C}$ to afford the fresh prepared diazonium salt (mixture A). In a separated 3-necked round-bottom flask, SO_2 was pumped into the stirred mixture of CuCl_2 (235 mg, 1.75 mmol) in acetic acid (20 mL) for 2 h at $20\text{ }^\circ\text{C}$ to afford mixture B. The mixture A was then added into the mixture B at $20\text{ }^\circ\text{C}$. The resulting mixture was stirred for additional overnight at $25\text{ }^\circ\text{C}$. The reaction mixture was diluted with water (40 mL), the precipitated solids were collected by filtration, washed with water (2 x 20 mL) and dried under vacuum to afford 4-(1,3-oxazol-2-yl)benzenesulfonyl chloride (1.20 g, 67%) as an off-white solid. LCMS (ES, m/z): 244, 246 $[\text{M}+\text{H}]^+$.

Step 2. tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate

[0254] To a stirred mixture of tert-butyl N-(prop-2-yn-1-yl)carbamate (5.00 g, 30.6 mmol) in DMF (50 mL) was added NaH (1.35 g, 33.7 mmol, 60%) in portions at $0\text{ }^\circ\text{C}$. The resulting mixture was stirred for 30 min at $0\text{ }^\circ\text{C}$ under nitrogen atmosphere. This was followed by the additional of 3-bromoprop-1-yne (4.60 g, 36.7 mmol). The resulting mixture was stirred for 3 h at $26\text{ }^\circ\text{C}$ under

nitrogen atmosphere. The reaction mixture was poured into water/ice (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (3 x 100 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (2.60 g, 42%) as a yellow oil. LCMS (ES, m/z): 194 [M+H]⁺.

Step 3. tert-butyl 6-(3-bromobenzoyl)-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0255] To a stirred mixture of tert-butyl N,N-bis(prop-2-yn-1-yl)carbamate (1.50 g, 7.76 mmol) and 3-bromobenzoyl cyanide (1.63 g, 7.76 mmol) in DCE (20 mL) was added chloro(1,5-cyclooctadiene)(pentamethylcyclopentadienyl)ruthenium(II) (236 mg, 0.62 mmol). The resulting mixture was stirred for 1 h at 60 °C under nitrogen atmosphere. The mixture was cooled to room temperature, poured into water/ice (40 mL) and extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford tert-butyl 6-(3-bromobenzoyl)-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (1.80 g, 55%) as a brown solid. LCMS (ES, m/z): 403, 405 [M+H]⁺.

Step 4. Tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate

[0256] To a solution of tert-butyl 6-(3-bromobenzoyl)-1H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.40 g, 5.95 mmol) in methanol (15 mL) and dichloromethane (15 mL) was added NaBH₄ (450 mg, 11.9 mmol) in portions at 0 °C. The resulting mixture was stirred for 1 h at room temperature. The mixture was concentrated and diluted with water (10 mL). The resulting mixture was extracted with dichloromethane (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The crude product was purified by silica gel chromatography (eluting with ethyl acetate/petroleum ether (1/1)) to afford tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate as a yellow oil (2.20 g, 91%). LCMS (ES, m/z): 405, 407 [M+H]⁺.

Step 5. (3-bromophenyl)((1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl))methanol hydrochloride

[0257] To a solution of tert-butyl 6-[(3-bromophenyl)(hydroxy)methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carboxylate (2.20 g, 5.43 mmol) in dichloromethane (20 mL) was added HCl (5 mL, 4

M in dioxane). The resulting solution was stirred for 3 h at room temperature. The mixture was concentrated under vacuum to afford (3-bromophenyl)({1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol hydrochloride as yellow solid (1.70 g, 91%). LCMS (ES, m/z): 305, 307 [M-HCl+H]⁺.

Step 6. (3-bromophenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol

[0258] To a stirred mixture of (3-bromophenyl)({1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol hydrochloride (1.68 g, 4.92 mmol) in dichloromethane (20 mL) was added TEA (6.85 mL, 67.7 mmol) and 4-(1,3-oxazol-2-yl)benzene-1-sulfonyl chloride (1.20 g, 4.93 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at room temperature. The mixture was concentrated under vacuum and the residue was diluted with of methanol (30 mL). The solids were collected by filtration and dried under vacuum to afford (3-bromophenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol as pink solid (2.00 g, 79%). LCMS (ES, m/z): 512, 514 [M+H]⁺.

Step 7. (S)-(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (first eluting isomer) and (R)-(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (second eluting isomer)

[0259] To a solution of (3-bromophenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol (100 mg, 0.19 mmol) in dioxane (5 mL) was added RuPhos 3 G (16 mg, 0.02 mmol), RuPhos (9 mg, 0.02 mmol), Cs₂CO₃ (191 mg, 0.56 mmol) and bis(2-methyl-2,6-diazaspiro[3.3]heptane); oxalic acid (66 mg, 0.21 mmol). The resulting mixture was stirred for 4 h at 110 °C. The reaction mixture was cooled to room temperature, poured into water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate concentrated under vacuum. The crude product was purified by Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 µm, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH₄HCO₃) and B: CH₃CN (10% to 40% in 7 min); Flow rate: 60 mL/min; Detector: UV 254 nm). The product fractions were concentrated under vacuum to afford the racemic product. The racemate was separated by Chiral Prep-HPLC with the following condition: Column: CHIRALPAK IC, 5 µm, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.1% DEA) and B: DCM (keep 50% B in 18 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; RT1: 10.692 min; RT2: 14.71 min.

The product fractions were concentrated and lyophilized to afford (S)-(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (first eluting isomer, RT1: 10.692 min) as a white solid (16.9 mg, 16%). And (R)-(3-[6-methyl-2,6-diazaspiro[3.3]heptan-2-yl]phenyl)([2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl])methanol (second eluting isomer, RT2: 14.71 min) as a white solid (15.2 mg, 15%).

[0260] First eluting isomer: ¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47-7.44 (m, 2H), 7.00-6.96 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 6.20 (d, J = 8.4 Hz, 1H), 5.96 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 3.6 Hz, 1H), 4.64-4.58 (m, 4H), 3.78 (s, 4H), 3.33-3.27 (m, 4H), 2.20 (s, 3H). LCMS (ES, m/z): 544 [M+H]⁺.

[0261] Second eluting isomer: ¹H-NMR (DMSO-d₆, 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47-7.44 (m, 2H), 7.00-6.96 (m, 1H), 6.58 (d, J = 7.6 Hz, 1H), 6.44 (s, 1H), 6.20 (d, J = 7.6 Hz, 1H), 5.96 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 4.0 Hz, 1H), 4.65-4.58 (m, 4H), 3.79-3.75 (m, 4H), 3.25 (s, 4H), 2.19 (s, 3H). LCMS (ES, m/z): 544 [M+H]⁺.

Table 15.

Cmpd. No.	Purification Methods
3 and 4	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (10% to 30% over 20 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The two enantiomers were further separated by Chiral Prep-HPLC (Column: CHIRALPAK IA, 5 μm, 20 x 250 mm; Mobile Phase, A: methanol and B: DCM (hold 50% B over 25 min); Detector: UV 254/220 nm; Retention time: 1 st , 7.62 min; 2 nd , 9.89 min)
5 and 6	CHIRALPAK IG, 20 x 250 mm, 5 mm; Mobile Phase A: MeOH (0.1% DEA), Mobile Phase B: DCM; Flow rate: 20 mL/min; Gradient: 50 B to 50 B in 10 min; 220/254 nm; Retention time: 1 st , 3.97; Retention time: 2 nd , 5.96
7	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (20% to 42% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
8	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (40% to 57% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
9	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 60% over 5.8 min); Flow rate: 20 mL/min; Detector: UV 254 nm)
10	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (30% to 58% over 7 min)
11	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (30% to 65% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
12	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: MeCN (25% to 38% over 8 min); Flow rate: 60 mL/min; Detector: UV 254 nm)
13	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μm, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: MeCN (25% to 65% over 8 min); Flow rate: 20 mL/min; Detector: UV 254 nm)

Cmpd. No.	Purification Methods
14 and 15	Prep HPLC (CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM (3:1, containing 0.1% isopropyl amine) and B: MeOH: DCM (1:1); Gradient: keep 30% B over 17 min; Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 8.426 min; 2 nd , 10.756 min)
17	prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (30% B to 62% B over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm)
18	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (40% to 62% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
19	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (30% to 65% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
20, 21, 22, and 23	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (5% to 5% over 3 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The four enantiomers were further separated by Chiral-Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.2% isopropyl amine) and B: isopropyl alcohol (hold 50% B over 25 min); Detector: UV 254/220 nm; Retention time: 1 st , 1.583 min; 2 nd , 2.189 min; 3 rd , 1.698 min; 4 th , 3.285 min)
25	XBridge Shield RP18 OBD Column, 5 μ m, 19x150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (20% to 40% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm).
26 and 27	CHIRALPAK IF, 5 μ m, 20x250 mm; Mobile Phase, A: MTBE (containing 0.2% IPA) and B: EtOH (keep 50% B over 25 min); Detector: UV 254/220 nm; Retention time: 1 st , 10.759 min; 2 nd , 17.742 min).
28	XBridge Shield RP18 OBD Column, 5 μ m, 19x150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (20% to 40% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm).
29 and 30	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 45% over 8 min); Flow rate: 20 mL/min; Detector: UV 254 nm). The product fractions were concentrated under vacuum. The two enantiomers were separated by Prep-Chiral-HPLC (Column: CHIRALPAK IF, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (containing 0.2% IPA) and B: EtOH (keep 50% B over 25 min); Detector: UV 254/220 nm; Retention time: 1 st , 8.583 min; 2 nd , 12.347 min)
31	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 45% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm)
32	Prep-HPLC (Column: XBridge Shield C18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 50% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
33	Prep-HPLC (Column: XBridge Prep OBD C18 Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (37% to 62% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
34	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (32% to 42% over 7 min); Flow rate: 60 mL/min; Detector: UV 254/220 nm)
35	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (15% to 45% over 7 min)
36	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 55% over 7 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm)
37	XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (30% to 50% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm).
38 and 39	Chiral Prep-HPLC (Column: CHIRALPAK IE, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (containing 0.1% TFA) and B: EtOH; Gradient: keep 5% B over 22 min; Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 15.705 min; 2 nd , 19.957 min)

Cmpd. No.	Purification Methods
40 and 41	Chiral Prep-HPLC (Column: CHIRALPAK IE, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (containing 0.2% IPA) and B: MeOH (keep 30% B over 14 min); Flow rate: 18 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 8.184 min; 2 nd , 10.819 min)
42 and 43	Prep-SFC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase A: CO ₂ , Mobile Phase B: EtOH:DCM = 1:1 (keep 50% B over 12 min); Flow rate: 40 mL/min; Detector, UV 220 nm; Retention time: 1 st , 8.33 min; 2 nd , 10.81 min)
44	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: MeCN (30% to 55% over 7 min); Flow rate: 60 mL/min; Detector: UV 254 nm)
45	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: MeCN (35% to 55% over 7 min); Flow rate: 60 mL/min; Detector: UV 254 nm)
46 and 47	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% DEA), B: EtOH; Gradient: keep 50% B over 24 min; Flow rate: 18 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 12.618 min; 2 nd , 19.401 min)
48 and 49	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (containing 0.2% DEA) and B: MeOH; Gradient: keep 50% B over 18 min; Flow rate: 20 mL/min; Detector: UV 220/254 nm; Retention time: 1 st , 9.22 min; 2 nd , 15.54 min)
50 and 51	Prep-HPLC (Column: XBridge Shield RP18 OBD Column, 5 μ m, 30 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (25% to 40% over 8 min); Flow rate: 60 mL/min; Detector: UV 254 nm)
52 and 53	Chiral Prep-HPLC (Column: CHIRAL ART Cellulose-SB, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (0.2% IPA) and B: MeOH (keep 20% B over 16 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 10.406 min; 2 nd , 13.941 min)
54	XBridge Shield RP18 OBD Column, 5 μ m, 19 x 150 mm; Mobile Phase, A: water (containing 10 mmol/L NH ₄ HCO ₃) and B: CH ₃ CN (22% to 37% over 7 min); Flow rate: 20 mL/min; Detector: UV 254 nm).
55 and 56	CHIRALPAK IC, 5 μ m, 20 x 150 mm; Mobile Phase, A: MeCN and B: water (containing 10 mmol/L NH ₄ HCO ₃) (keep 20% B over 12 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 5.931 min; 2 nd , 10.037 min).
57 and 58	Chiral Prep-HPLC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.1% DEA) and B: DCM (keep 50% B in 35 min); Flow rate: 16 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 19.689 min; 2 nd , 29.857 min)
59 and 60	Chiral Prep-HPLC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (0.2% IPA) and B: EtOH (keep 50% B over 25 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 10.086 min; 2 nd , 17.541 min)
61, 62, 63, and 64	Chiral Prep-HPLC (CHIRALPAK IC, 2 x 25 cm, 5 μ m; Mobile Phase A: Hexane: DCM = 3:1 (containing 0.1% DEA), Mobile Phase B: isopropanol; Flow rate: 20 mL/min; Gradient: keep 30% B over 30 min; Detector: 220/254 nm; Rt: 1 st :17.624 min; 2 nd : 23.93 min)
65, 66, 67, and 68	Chiral Prep-HPLC (CHIRALPAK IC, 2 x 25 cm, 5 μ m; Mobile Phase A: MTBE (containing 0.1% IPA), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: keep 10% B over 20 min; Detector: 220/254 nm; Rt: 1 st : 7.451 min; 2 nd : 10.399 min)
69 and 70	Chiral Prep-HPLC (Column: CHIRALPAK IC, 2 x 25cm, 5 μ m; Mobile Phase A: MTBE (containing 0.1% DEA), Mobile Phase B: MeOH; Flow rate: 20 mL/min; Gradient: 50 B to 50 B in 18 min; Detector: 220/254 nm; RT: 1 st : 8.833 min; 2 nd : 13.602 min)
71 and 72	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH (containing 0.1% DEA) and B: DCM (keep 40% B in 15 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 10.772 min; 2 nd , 13.314 min)
73 and 74	Chiral Prep-HPLC (Column: CHIRALPAK IC, 2 x 25 cm, 5 μ m; Mobile Phase A: MeOH, Mobile Phase B: DCM; Flow rate: 15 mL/min; Gradient: keep 30% B over 30 min; Detector: UV 254/220 nm; Rt: 1 st , 13.818 min; 2 nd , 25.13 min)
75	Chiral Prep-HPLC (Column: CHIRALPAK IF, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH (containing 0.1% DEA) and B: DCM (keep 50% B over 28 min); Detector: UV 254/220 nm; Retention time: 1 st , 12.7 min; 2 nd , 22.3 min)

Cmpd. No.	Purification Methods
76 and 77	Chiral Prep-HPLC (Column: CHIRALPAK IF, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.1% DEA) and B: DCM; Gradient: keep 30% B over 18 min; Detector: UV 254/220 nm; Retention time: 1 st , 8.2 min; 2 nd , 10.215 min)
78 and 79	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH (containing 0.1% ammonia) and B: DCM (keep 50% B over 11 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 6.831 min; 2 nd , 8.288 min)
82 and 83	Chiral Prep-HPLC (Column: CHIRALPAK IC, 2 x 25cm, 5 μ m; Mobile Phase, A: MTBE (containing 0.2% IPA) and B: MeOH; Flow rate: 20 mL/min; Gradient: keep 50% B over 13 min; Detector: UV 254/220 nm; Retention time: 1 st , 8.541 min; 2 nd , 9.831 min)
84 and 85	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: methanol (containing 0.1% DEA) and B: DCM (keep 50% B over 18 min); Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 10.692 min; 2 nd , 14.71 min)
86, 87, 88, and 89	Chiral Prep-HPLC (Column: CHIRALPAK IA, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE (containing 0.1% IPA) and B: ethanol (keep 50% B over 60 min); Flow rate: 13 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 18.353 min; 2 nd , 22.077 min; 3 rd , 30.765 min; 4 th , 47.141 min)
90 and 91	CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MTBE(0.2%IPA)--HPLC and B: EtOH--HPLC (keep 40% B over 14 min); Flow rate: 17 mL/min; Detector: UV 220/254 nm; Retention time: 1 st , 7.122 min; 2 nd , 11.298 min).
92, 93, 94, and 95	Chiral Prep-HPLC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% IPA) and B: MeOH: DCM = 1:1; Gradient: keep 70% B over 14 min; Flow rate: 20 mL/min; Detector: UV 220/254 nm; Retention time: 3 rd , 17.159 min; 4 th , 10.963 min)
96 and 97	Chiral Prep-HPLC (Column: CHIRALPAK IG, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% IPA) and B: MeOH; Gradient: keep 40% B over 22 min; Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 15.522 min; 2 nd , 19.584 min)
98 and 99	Chiral Prep-HPLC (Column: CHIRAL ART Cellulose-SB, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH (containing 0.1% DEA) and B: DCM; Gradient: keep 15% B over 22 min; Flow rate: 20 mL/min; Detector: UV 254/220 nm; Retention time: 1 st , 11.342 min; 2 nd , 17.438 min)
100 and 101	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% DEA) and B: MeOH: DCM = 1:1 (keep 50% B over 20 min); Flow rate: 20 mL/min; Detector: UV 220/254 nm; Retention time: 1 st , 11.313 min; 2 nd , 15.462 min)
102 and 103	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: MeOH and B: DCM; Gradient: keep 50% B over 12 min; Flow rate: 20 mL/min; Detector: UV 220/254 nm; Retention time: 1 st , 6.744 min; 2 nd , 9.757 min)
104 and 105	CHIRALPAK IF, 5 μ m, 20 x 250 mm; Mobile Phase A:HEX:DCM=3:1(0.2%IPA), Mobile Phase B: EtOH (keep 50% B over 17 min); Detector: UV 254/220 nm; Retention time: 1 st , 6.956 min; 2 nd , 13.145 min).
106 and 107	Chiral Prep-HPLC (Column: CHIRALPAK IC, 5 μ m, 20 x 250 mm; Mobile Phase, A: hexane: DCM = 3:1 (containing 0.1% DEA) and B: MeOH: DCM = 1:1; Gradient: keep 60% B over 10 min; Flow rate: 20 mL/min; Detector: UV 220/254 nm; Retention time: 1 st , 6.446 min; 2 nd , 8.034 min)

Example 3. Biochemical Assay for USP9X Inhibition

[0262] The assay was performed in a final volume of 6 μ L assay buffer containing 20 mM Tris-HCl (pH 8.0, (1M Tris-HCl, pH 8.0 solution; Corning 46-031-CM)), L-Glutathione (GSH) reducing agent (1 mM, Sigma-Aldrich, G4251-100G), 0.03% Bovine Gamma Globulin (BGG) (0.22 μ M filtered, Sigma, G7516-25G), and 0.01% Triton X-100 (Sigma, T9284-10L). DMSO solutions of the compounds in nanoliter quantities (10-point, 3-fold serial dilutions) were dispensed into 1536 assay plates (Corning, #3724BC) for final test concentrations of 25 μ M to 1.3 nM, top to lowest dose, respectively. Concentration and incubation times were optimized for the maximal signal-to-background while maintaining initial velocity conditions at a fixed substrate concentration ($\ll K_m$).

The final concentration of USP9X (Enzyme, E) was 0.025 nM, and the final concentration of Ubiquitin-Rhodamine 110 (Ub-Rh110, UbiQ-126) (Substrate, S) was 25 nM. To assay plates (pre-stamped with compound) was added 3 μ L 2x Enzyme. The enzyme was preincubated for 30 minutes and then treated with 3 μ L of 2x Substrate. Plates were incubated for 11 min (continuous kinetic read) at room temperature before the fluorescence was read on the Envision plate reader (Perkin Elmer) or PheraSTAR plate reader (BMG), with excitation at 485 nm and emission at 535 nm. The slope (best fit linear regression) of the five reads was used to normalize for inhibition. For all assays, data are reported as percent inhibition compared with control wells based on the following equation: %inh = $100 * ((\text{FLU} - \text{AveLow}) / (\text{AveHigh} - \text{AveLow}))$, wherein FLU is measured Fluorescence, AveLow is average Fluorescence of no enzyme control (n=64), and AveHigh is average Fluorescence of DMSO control (n=64). IC₅₀ values are determined by curve fitting of the standard 4 parameter logistic fitting algorithm included in the Activity Base software package: IDBS XE Designer Model205. Data are fitted using the Levenburg Marquardt algorithm.

[0263] As set forth in Tables 16 and 17, IC₅₀ values are defined as follows: > 25 μ M (--); $\leq$ 25 μ M and > 10 μ M (+); $\leq$ 10 μ M and > 1 μ M (++); $\leq$ 1 μ M and > 0.1 μ M (+++); $\leq$ 0.1 μ M and > 0.001 μ M (++++).

[0264] In Tables 16 and 17, absolute stereochemistry has not been determined for some Examples. Accordingly, assignment of any Examples as the “R” or “S” stereoisomer is arbitrary, unless otherwise noted. In some cases, Examples are labeled with “1st eluting isomer”, “2nd eluting isomer”, etc. based on the purification method used to separate the stereoisomers (see Table 15).

Table 16.

Cmpd. No.	IC ₅₀ (μ M)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
1 (1 st eluting isomer)	++			(S)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-2,3-dihydro-1H-isindol-5-yl](phenyl)methanol;	424.0	(CD ₃ OD, 400 MHz) δ (ppm): 7.34-7.18 (m, 9H), 7.15-7.13 (m, 1H), 6.98-6.96 (m, 1H), 5.72 (s, 1H), 4.53 (s, 4H), 4.29-4.24 (m, 4H).
2 (2 nd eluting isomer)	+++			(R)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-2,3-dihydro-1H-isindol-5-yl](phenyl)methanol		
3 (1 st eluting isomer)	+++	8-10, 15-1	I	(S)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)methanol;	425.0	(Methanol-d ₄ , 300 MHz) δ (ppm): 8.34-8.29 (m, 1H), 7.53-7.49 (m, 1H), 7.42-7.17 (m, 7H), 7.04-6.95 (m, 1H), 5.79 (s, 1H), 4.64 (s, 4H), 4.35-4.22 (m, 4H).
4	+++			(R)-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-		

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
(2 nd eluting isomer)				c]pyridin-6-yl](phenyl)methanol		
5 (1 st eluting isomer)	+++	8-2, 1-1	A	[(2S)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl](methyl)amine; [(2R)-2-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-2-phenylethyl](methyl)amine	452.0	(400 MHz, Methanol-d ₄) δ 8.40 (d, J = 1.1 Hz, 1H), 7.36 – 7.16 (m, 7H), 7.17 (s, 1H), 6.99 – 6.92 (m, 1H), 4.60 (d, J = 2.0 Hz, 2H), 4.56 – 4.47 (m, 2H), 4.35 (dd, J = 8.8, 6.3 Hz, 1H), 4.26 (tt, J = 5.0, 2.6 Hz, 4H), 3.51 (dd, J = 12.2, 8.8 Hz, 1H), 3.17 (dd, J = 12.1, 6.3 Hz, 1H), 2.44 (s, 3H).
6 (2 nd eluting isomer)	+++					
7	++++	3-1, 4-1, 10-1	C	[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(piperazin-1-yl)phenyl]methanol	509.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.30 (s, 1H), 7.49 (s, 1H), 7.40-7.27 (m, 2H), 7.21-7.10 (m, 1H), 7.08-7.01 (m, 1H), 6.99-6.94 (m, 1H), 6.88-6.79 (m, 2H), 5.71 (s, 1H), 4.59 (s, 4H), 4.36-4.20 (m, 4H), 3.16-3.07 (m, 4H), 3.01-2.91 (m, 4H).
8	+++	10-1, 8-9	C	(3-chlorophenyl)[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]methanol	459.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.33 (s, 1H), 7.48 (s, 1H), 7.46-7.37 (m, 1H), 7.36-7.17 (m, 5H), 7.01 (d, J = 8.4 Hz, 1H), 6.31-6.18 (m, 1H), 5.75-5.62 (m, 1H), 4.62-4.45 (m, 4H), 4.34-4.16 (m, 4H).
9	+++	6-1, 9-2, 8-7	D	{3-[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl]-3-phenylpropyl}(methyl)amine	466.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.35 (s, 1H), 7.38-7.22 (m, 7H), 7.22-7.13 (m, 1H), 7.01-6.94 (m, 1H), 4.57 (s, 2H), 4.52 (s, 2H), 4.32-4.22 (m, 4H), 4.13 (t, J = 7.6 Hz, 1H), 2.53-2.43 (m, 2H), 2.47-2.33 (m, 1H), 2.33 (s, 3H), 2.28-2.21 (m, 1H).
10	+++	13-1	G	[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl](phenyl)methanamine	424.0	(DMSO-d ₆ , 300 MHz) δ (ppm): 8.34 (s, 1H), 7.41 (s, 1H), 7.35-7.21 (m, 6H), 7.17-7.12 (m, 1H), 7.04-7.01 (m, 1H), 5.08 (s, 1H), 4.53 (s, 4H), 4.29-4.25 (m, 4H), 2.41 (s, 2H).
11	+++	6-1	E	{[2-(2,3-dihydro-1,4-benzodioxine-6-sulfonyl)-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-	438.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.37 (s, 1H), 7.40-7.18 (m, 8H), 7.00-6.93 (m, 1H), 4.79 (s, 1H), 4.62-4.53

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				yl(phenyl)methyl(methyl)amine		(m, 4H), 4.31-4.21 (m, 4H), 2.31 (s, 3H).
12	+++	1-1, 8-3, 7-2	A	(2-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}-2-phenylethyl)(methyl)amine	478.0	(CD ₃ OD, 400 MHz) δ (ppm): 8.45 (s, 1H), 8.20 (m, 1H), 8.19-8.06 (m, 1H), 7.92-7.89 (m, 1H), 7.86-7.81 (m, 2H), 7.32-7.16 (m, 6H), 6.62-6.60 (m, 1H), 4.74 (s, 2H), 4.65 (s, 2H), 4.39-4.35 (m, 1H), 3.54-3.49 (m, 1H), 3.20-3.15 (m, 1H), 2.42 (s, 3H).
13	+++	6-1, 7-2, 8-6, 9-1	D	(3-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}-3-phenylpropyl)(methyl)amine	492.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.40 (s, 1H), 8.20 (s, 1H), 8.11-8.07 (m, 1H), 7.92-7.89 (m, 1H), 7.85-7.81 (m, 2H), 7.33-7.22 (m, 5H), 7.18-7.14 (m, 1H), 6.61 (s, 1H), 4.72-4.68 (d, J = 16.0 Hz, 4H), 4.16-4.12 (m, 1H), 2.53-2.49 (m, 2H), 2.45-2.31 (m, 4H), 2.29-2.22 (m, 1H).
14 (1 st eluting isomer)	++++	7-2, 8-4, 4-13	B	(R)-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol;	535.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.33-8.31 (m, 1H), 8.29-8.28 (m, 1H), 8.10-8.08 (m, 1H), 8.06-8.00 (m, 1H), 7.87-7.83 (m, 2H), 7.47 (s, 1H), 7.06-7.04 (m, 1H), 6.96-6.93 (m, 1H), 6.72-6.70 (m, 2H), 6.63-6.62 (m, 1H), 6.01-5.99 (m, 1H), 5.61-5.99 (m, 1H), 4.72-4.64 (m, 4H), 2.99-2.94 (m, 4H), 2.97-2.82 (m, 4H), 2.33-2.18 (m, 1H).
15 (2 nd eluting isomer)	++++			(S)-{2-[3-fluoro-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol		
16	+++	6-1, 8-5, 14-1	C	{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol		
17	+++	11-1, 6-1	F	{2-[4-(5-fluoro-1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol	451.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.33 (s, 1H), 8.07-7.98 (m, 2H), 7.88-7.85 (m, 2H), 7.74-7.73 (m, 1H), 7.49 (s, 1H), 7.31 (d, J = 6.8 Hz, 2H), 7.24-7.21 (m, 2H), 7.17-7.14 (m, 1H), 6.30-6.29 (m, 1H), 6.08-6.06 (m, 1H), 5.64 (d, J = 4.0 Hz, 1H), 4.69-4.57 (m, 4H).
18	+	6-1, 5-1	C	{2-[3-methoxy-4-(1H-pyrazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-	463.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.34 (s, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.93-7.77

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				c]pyridin-6-yl}(phenyl)methanol		(m, 1H), 7.76 (s, 1H), 7.59-7.56 (m, 1H), 7.53-7.50 (m, 2H), 7.33 (d, J = 7.2 Hz, 2H), 7.25-7.21 (m, 2H), 7.18-7.14 (m, 1H), 6.53-6.52 (m, 1H), 6.09-6.07 (m, 1H), 5.69-5.67 (m, 1H), 4.73-4.61 (m, 4H), 3.97 (s, 3H).
19	--	6-1, 7-1	C	{2-[4-(1H-imidazol-1-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol	433.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.38 (s, 1H), 8.34 (s, 1H), 7.99-7.91 (m, 2H), 7.88-7.84 (m, 3H), 7.49 (s, 1H), 7.33-7.31 (m, 2H), 7.25-7.21 (m, 2H), 7.18-7.13 (m, 2H), 6.08 (d, J = 4.4 Hz, 1H), 5.67 (d, J = 4.0 Hz, 1H), 4.66-4.58 (m, 4H).
20 (1 st eluting isomer)	--	6-1, 17-1, 8-13	C	(S)-phenyl(2-{[(1r,4r)-4-(1H-pyrazol-1-yl)cyclohexyl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol; (S)-phenyl(2-{[(1s,4s)-4-(1H-pyrazol-1-yl)cyclohexyl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol; (R)-phenyl(2-{[(1r,4r)-4-(1H-pyrazol-1-yl)cyclohexyl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol; (R)-phenyl(2-{[(1s,4s)-4-(1H-pyrazol-1-yl)cyclohexyl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol	439.0	1 st : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.42 (s, 1H), 7.79 (s, 1H), 7.57 (s, 1H), 7.45 (s, 1H), 7.40-7.38 (m, 2H), 7.31-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.26 (s, 1H), 6.13 (s, 1H), 5.74 (s, 1H), 4.70-4.65 (m, 4H), 4.32 (s, 1H), 3.56-3.53 (m, 1H), 2.42-2.33 (m, 2H), 1.85-1.84 (m, 6H).
21 (2 nd eluting isomer)	--					2 nd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.43 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.58-7.41 (m, 3H), 7.30-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.26-6.21 (m, 1H), 6.14-6.13 (m, 1H), 5.75 (s, 1H), 4.74 (s, 4H), 4.23-4.17 (m, 1H), 3.49-3.44 (m, 1H), 2.15-1.99 (m, 4H), 1.84-1.67 (m, 4H).
22 (3 rd eluting isomer)	++					3 rd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.42 (s, 1H), 7.78 (s, 1H), 7.57 (s, 1H), 7.45-7.38 (m, 3H), 7.31-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.26 (s, 1H), 6.13-6.12 (m, 1H), 5.74-5.73 (m, 1H), 4.70 (s, 4H), 4.32 (s, 1H), 3.55 (s, 1H), 2.39-2.33 (m, 2H), 1.85-1.84 (m, 6H).
23 (4 th eluting isomer)	--					4 th : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.43 (s, 1H), 7.68 (s, 1H), 7.58 (s, 1H), 7.47-7.39 (m, 3H), 7.30-7.27 (m, 2H), 7.22-7.18 (m, 1H), 6.21 (s,

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
						1H), 6.14-6.13 (m, 1H), 5.75-5.74 (m, 1H), 4.74 (s, 4H), 4.23-4.17 (m, 1H), 3.50-3.44 (m, 1H), 2.15-2.00 (m, 4H), 1.84-1.67 (m, 4H).
24	--	8-12, 16-1	J	phenyl(2-{[1-(1,3-thiazol-2-yl)piperidin-4-yl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol	457.3	
25	++++	4-13, 8-11	B	{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol	518.0	(DMSO-d ₆ , 300 MHz) δ (ppm): 8.36 (s, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 14.0 Hz, 2H), 7.10 – 7.06 (m, 1H), 6.99 (s, 1H), 6.77 – 6.72 (m, 2H), 5.60 (s, 1H), 4.68 – 4.58 (m, 4H), 3.19 (s, 4H), 3.07 (m, 4H).
26 (1 st eluting isomer)	++++	8-11, 3-3	D	(R)-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol;	518.0	(DMSO-d ₆ 400 MHz) δ (ppm): 8.32 (d, J = 4.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.47 (s, 2H), 7.05-7.01 (m, 1H), 6.95 (s, 1H), 6.71-6.66 (m, 2H), 5.97 (d, J = 3.2 Hz, 1H), 5.59 (s, 1H), 4.69-4.58 (m, 4H), 2.98-2.96 (m, 4H), 2.85-2.78 (m, 4H).
27 (2 nd eluting isomer)	++++			(S)-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol		
28	++++	8-11, 4-13	J	[3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol	532.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (d, J = 4.4 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47 (s, 2H), 7.06-7.02 (m, 1H), 6.96 (s, 1H), 6.73-6.66 (m, 2H), 5.97 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 4.65-4.59 (m, 4H), 3.07-3.05 (m, 4H), 2.47-2.33 (m, 4H), 2.20 (s, 3H).
29 (1 st eluting isomer)	++++	4-13, 8-11	J	(R)-[3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	532.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (d, J = 4.4 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47 (s, 2H), 7.06-7.02 (m, 1H), 6.96 (s, 1H), 6.73-6.66 (m, 2H), 5.97 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 4.65-4.59 (m, 4H), 3.07-3.05 (m, 4H), 2.47-2.33 (m, 4H), 2.20 (s, 3H).
30 (2 nd eluting isomer)	++++			(S)-[3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
31	++++	2-1, 8-14, 4-13	B	{2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}[3-(piperazin-1-yl)phenyl]methanol	536.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.35 (d, J = 16.8 Hz, 2H), 8.24-8.22 (m, 1H), 7.90-7.83 (m, 2H), 7.52 (s, 1H), 7.47 (s, 1H), 7.06-7.02 (m, 1H), 6.95 (s, 1H), 6.76-6.67 (m, 2H), 5.98 (d, J = 4.0 Hz, 1H), 5.60 (d, J = 4.0 Hz, 1H), 4.73-4.62 (m, 4H), 2.98-2.81 (m, 4H), 2.80-2.70 (m, 4H), 2.57-2.54 (m, 1H).
32	--	8-8, 4-2	H	(2-{[1-(1,3-oxazol-2-yl)piperidin-4-yl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)(phenyl)methanol	441.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.43 (s, 1H), 7.63 (s, 1H), 7.43-7.41 (m, 3H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 6.84 (s, 1H), 5.85 (s, 1H), 4.92-4.83 (s, 4H), 4.15-4.11 (m, 2H), 3.59-3.52 (m, 1H), 3.08-3.01 (m, 2H), 2.16-2.12 (m, 2H), 1.91-1.85 (m, 2H).
33	++++	18-1, 2-2	F	{7-methyl-2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol	448.0	(DMSO-d ₆ , 400 MHz,) δ (ppm): 8.33-8.29 (m, 2H), 8.17 (d, J = 8.4 Hz, 2H), 8.04-8.02 (m, 2H), 7.48 (s, 1H), 7.22-7.17 (m, 5H), 5.90-5.86 (m, 2H), 4.69-4.63 (m, 4H), 2.06 (s, 3H).
34	+++	19-1, 2-2	F	{6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-c]pyridazin-3-yl}(phenyl)methanol	435.0	(400 MHz, DMSO-d ₆) δ (ppm): 8.32 (s, 1H), 8.14 (d, J = 8.6 Hz, 2H), 8.03 (d, J = 8.3 Hz, 2H), 7.69 (s, 1H), 7.47 (s, 1H), 7.34 (d, J = 7.3 Hz, 2H), 7.26 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 6.6 Hz, 1H), 6.39 (d, J = 4.2 Hz, 1H), 5.96 (d, J = 4.0 Hz, 1H), 4.85-4.69 (m, 4H).
35	++++	21-1, 2-2, 8-15	A	2,3-dihydro-1H-isoindol-4-yl({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol	475.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (d, J = 3.2 Hz, 2H), 8.21-8.15 (m, 2H), 8.04-7.97 (m, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.26-7.03 (m, 3H), 6.14-6.02 (m, 1H), 5.68-5.65 (m, 1H), 4.71-4.56 (m, 5H), 4.15-3.95 (m, 3H).
36	++++	2-1, 20-1	F	{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}(phenyl)methanol	453.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.65 (s, 1H), 8.39 (s, 1H), 8.21 (t, J = 8.0 Hz, 1H), 7.96-7.93 (m, 1H), 7.88-7.85 (s, 1H), 7.53 (s, 1H), 7.44-7.36 (m, 2H), 7.26-7.22 (m,

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
						2H), 7.20-7.15 (m, 1H), 5.98-5.95 (m, 1H), 5.74-5.72 (m, 1H), 4.71-4.66 (m, 4H).
37	++++			1-[3-(1-{2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}ethyl)phenyl]piperazine	534.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.39 (s, 2H), 8.23-8.19 (m, 1H), 7.90-7.87 (m, 1H), 7.84-7.81 (m, 1H), 7.53 (s, 1H), 7.17 (s, 1H), 7.05-7.01 (m, 1H), 6.84 (s, 1H), 6.69-6.66 (m, 1H), 6.62-6.59 (m, 1H), 4.65-4.63 (m, 4H), 4.15-4.14 (m, 1H), 2.97 (s, 4H), 2.79 (s, 4H), 1.51 (d, J = 7.2 Hz, 3H).
38 (1 st eluting isomer)	++++	20-2, 2-1	F	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}(3-methoxyphenyl)methanol;	483.0	(CDCl ₃ , 400 MHz) δ (ppm): 8.63 (br s, 1H), 8.30-8.21 (m, 1H), 7.86 (s, 1H), 7.79-7.75 (m, 2H), 7.39 (s, 1H), 7.29-7.22 (m, 1H), 7.04-7.00 (m, 2H), 6.81-6.80 (m, 1H), 5.96-5.86 (m, 1H), 4.83-4.67 (m, 4H), 3.79 (s, 3H).
39 (2 nd eluting isomer)	++++			(R)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}(3-methoxyphenyl)methanol		
40 (1 st eluting isomer)	++++	2-1, 4-6, 8-19, 30-1	A	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(piperazin-1-yl)phenyl]methanol	537.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.65 (s, 1H), 8.38 (s, 1H), 8.24-8.20 (m, 1H), 7.96-7.93 (m, 1H), 7.88-7.86 (m, 1H), 7.53 (s, 1H), 7.10-7.00 (m, 2H), 6.78-6.69 (m, 2H), 5.87 (s, 1H), 5.66 (s, 1H), 4.69-4.66 (m, 4H), 3.03-3.01 (m, 4H), 2.87-2.85 (m, 4H).
41 (2 nd eluting isomer)	++++			(R)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(piperazin-1-yl)phenyl]methanol		
42 (1 st eluting isomer)	++++	3-2, 4-3, 8-16	C	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol;	551.0	(CDCl ₃ , 400 MHz) δ (ppm): 8.60 (s, 1H), 8.31-8.27 (m, 1H), 7.85 (s, 1H), 7.79-7.75 (m, 2H), 7.38 (s, 1H), 7.22-7.18 (m, 1H), 7.06-7.02 (m, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.83-6.80 (m, 1H), 5.82 (s, 1H), 4.79-4.63 (m, 5H), 3.25-3.22 (m, 4H), 2.62 (br s, 4H), 2.39 (s, 3H).
43 (2 nd eluting isomer)	++++			(R)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol		
44	++	4-9, 31-2	F	cyclopentyl({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol	427.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.63 (s, 1H), 8.32 (s, 1H), 8.18-8.11 (m, 2H), 8.08-8.01 (m, 2H), 7.47 (s,

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
						1H), 5.13 (d, J = 8.0 Hz, 1H), 4.72 (s, 2H), 4.64 (s, 2H), 4.32-4.29 (m, 1H), 2.30-3.23 (m, 1H), 1.59-1.32 (m, 6H), 1.21-1.12 (m, 1H), 1.09-1.01 (m, 1H).
45	++	4-7, 31-1	F	cyclohexyl({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol	441.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.64 (s, 1H), 8.32 (s, 1H), 8.19-8.12 (m, 2H), 8.08-8.02 (m, 2H), 7.47 (s, 1H), 4.99 (d, J = 8.0 Hz, 1H), 4.72 (s, 2H), 4.64-4.63 (m, 2H), 4.26 (t, J = 8.0 Hz, 1H), 175-7.68 (m, 1H), 1.62-1.60 (m, 2H), 1.53-1.49 (m, 2H), 1.15-1.07 (m, 2H), 1.07-0.99 (m, 3H), 0.96-0.86 (m, 1H).
46 (1 st eluting isomer)	++	24-4, 32-1	K	(S)-{2-[4-(4,5-dihydro-1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol;	436.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.95 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.19-7.16 (m, 1H), 6.08 (d, J = 4.0 Hz, 1H), 5.67 (d, J = 4.0 Hz, 1H), 4.71-4.54 (m, 4H), 4.43 (t, J = 8.0 Hz, 2H), 3.98 (t, J = 8.0 Hz, 2H).
47 (2 nd eluting isomer)	++			(R)-{2-[4-(4,5-dihydro-1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}(phenyl)methanol		
48 (1 st eluting isomer)	++++	24-3, 8-18	C	(S)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	546.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 5.99 (d, J = 4.0 Hz, 1H), 5.60 (d, J = 4.0 Hz, 1H), 4.68-4.59 (m, 4H), 2.76-2.74 (m, 4H), 2.54-2.50 (m, 4H), 2.22 (s, 3H), 2.13 (s, 3H).
49 (2 nd eluting isomer)	++++			(R)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		
50 (1 st eluting isomer)	++++	27-1, 25-3, 3-5, 4-11, 33-1	F	(S)-{3-[(3S)-3,4-dimethylpiperazin-1-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol;	547.0	1 st : (CDCl ₃ , 400 MHz) δ (ppm): 8.57 (s, 1H), 8.28-8.23 (m, 2H), 8.00 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.32 (s, 1H), 7.29-7.18 (m, 1H), 7.02 (s, 1H), 6.93 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.81 (s, 1H), 4.77-4.62 (m, 4H), 4.53 (s, 1H), 3.56-3.47 (m, 2H), 3.02 (s, 2H), 2.42 (s, 6H), 1.21 (s, 3H).
				(R)-{3-[(3S)-3,4-dimethylpiperazin-1-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-		

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
51 (2 nd eluting isomer)	++++			d]pyrimidin-2-yl))methanol; (S)-{3-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol; (R)-{3-[(3R)-3,4-dimethylpiperazin-1-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol		2 nd : (CDCl ₃ , 400 MHz) δ (ppm): 8.58 (s, 1H), 8.25-8.23 (m, 2H), 8.00 (d, J = 8.0 Hz, 2H), 7.80 (s, 1H), 7.32 (s, 1H), 7.28-7.19 (m, 1H), 7.04 (s, 1H), 6.96 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 5.82 (s, 1H), 4.73-4.62 (m, 4H), 4.55 (s, 1H), 3.55-3.52 (m, 2H), 3.02 (s, 2H), 2.42 (s, 6H), 1.21 (s, 3H).
52 (1 st eluting isomer)	++++	27-1, 3-6, 4-12, 8-20, 33-1	C	(S)-{3-[(8aS)-octahydropyrrolo[1,2-a]piperazin-2-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol; (R)-{3-[(8aS)-octahydropyrrolo[1,2-a]piperazin-2-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol;	559.0	1 st : (CDCl ₃ , 400 MHz) δ (ppm): 8.58 (s, 1H), 8.24 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.32 (s, 1H), 7.22-7.18 (m, 1H), 7.07 (s, 1H), 6.93 (s, 1H), 6.83-6.81 (m, 1H), 5.81 (s, 1H), 4.77-4.71 (m, 2H), 4.67-4.62 (m, 2H), 4.51 (s, 1H), 3.75 (s, 1H), 3.60 (d, J = 12.4 Hz, 1H), 3.17 (s, 2H), 3.10-2.85 (m, 1H), 1.96-1.92 (m, 3H), 1.59 (s, 4H), 1.218 (s, 1H).
53 (2 nd eluting isomer)	++++			(S)-{3-[(8aR)-octahydropyrrolo[1,2-a]piperazin-2-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol; (R)-{3-[(8aR)-octahydropyrrolo[1,2-a]piperazin-2-yl]phenyl}({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl))methanol		2 nd : (CDCl ₃ , 400 MHz) δ (ppm): 8.57 (s, 1H), 8.24 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.32 (s, 1H), 7.22-7.18 (m, 1H), 7.07 (s, 1H), 6.92 (d, J = 7.2 Hz, 1H), 6.83-6.81 (m, 1H), 5.81 (s, 1H), 4.77-4.73 (m, 2H), 4.67-4.62 (m, 2H), 4.51 (s, 1H), 3.76-3.71 (m, 1H), 3.63 (d, J = 12.0 Hz, 1H), 3.18 (s, 2H), 3.03-2.90 (m, 1H), 2.76-2.25 (m, 2H), 1.96-1.88 (m, 3H), 1.84-1.63 (m, 3H).
54	++++			2-[3-(4-methylpiperazin-1-yl)phenyl]-2-{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}acetonitrile	541.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.47 (s, 1H), 8.32 (s, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.35 (s, 1H), 7.17-7.15 (m, 1H), 6.97 (s, 1H), 6.85-6.83 (m, 1H), 6.72-6.70 (m, 1H), 5.75 (s, 1H), 4.66 (s, 4H), 3.10-3.08 (m, 4H), 2.43-2.40 (m, 4H), 2.21 (s, 3H).

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
55 (1 st eluting isomer)	+++			(2S)-2-(3-methoxyphenyl)-N-methyl-2-[6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]acetamide;	506.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.62 (s, J = 0.8 Hz, 1H), 8.33 (s, J = 1.2 Hz, 1H), 8.17-8.15 (m, 2H), 8.06-8.04 (m, 2H), 7.94-7.92 (m, 1H), 7.47 (s, J = 0.8 Hz, 1H), 7.19-7.16 (m, 1H), 6.93-6.89 (m, 1H), 6.87-6.81 (m, 1H), 6.80-6.79 (m, 1H), 5.10 (s, J = 0.8 Hz, 1H), 4.67-4.61 (m, 4H), 3.71-3.68 (m, 3H), 2.52 (s, J = 1.6 Hz, 3H).
56 (2 nd eluting isomer)	+++					
57 (1 st eluting isomer)	+++	2-1, 27-1, 8-21, 34-1, 35-1	D	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]}(2-[(methylamino)methyl]quinolin-8-yl)methanol;	547.0	(CDCl ₃ , 400 MHz) δ (ppm): 8.68 (s, 1H), 8.26-8.23 (m, 1H), 8.15 (d, J = 8.8 Hz, 1H), 7.84-7.72 (m, 5H), 7.57-7.53 (m, 1H), 7.37-7.32 (m, 3H), 6.57 (s, 1H), 4.71 (s, 2H), 4.64 (s, 2H), 4.23-4.11 (m, 2H), 2.69 (s, 2H).
58 (2 nd eluting isomer)	++++					
59 (1 st eluting isomer)	++++	2-1, 27-1, 33-2, 32-2	A	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl]}(2,3,4,5-tetrahydro-1,4-benzoxazepin-9-yl)methanol;	524.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.63 (s, 1H), 8.39 (s, 1H), 8.24-8.21 (m, 1H), 7.98-7.95 (m, 1H), 7.89-7.87 (m, 1H), 7.53 (s, 1H), 7.39-7.36 (m, 1H), 7.06-7.04 (m, 1H), 6.96-6.92 (m, 1H), 5.98 (d, J = 5.6 Hz, 1H), 5.85 (d, J = 6.0 Hz, 1H), 4.72-4.63 (m, 4H), 3.71 (s, 2H), 3.52-3.45 (m, 1H), 3.34-3.25 (m, 2H), 2.90-2.81 (m, 2H).
60 (2 nd eluting isomer)	+++					
61 (1 st eluting isomer)	++++	2-1, 22-2, 3-7, 36-1	F	(S)-[(3S)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol;	564.0	1 st : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.03-6.93 (m, 2H), 6.71-6.68 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.07 (br s, 4H), 2.50-2.48 (m, 4H), 2.26 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
62	++++					2 nd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.32 (s,

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
(2 nd eluting isomer)				(4-methylpiperazin-1-yl)phenyl]methanol; (S)-[(3R)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol		1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 7.03-6.93 (m, 2H), 6.71-6.68 (m, 1H), 6.65-6.62 (m, 1H), 6.02 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.06-3.04 (m, 4H), 2.43 (br s, 4H), 2.22 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H).
63 (3 rd eluting isomer)	++++					3 rd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.37 (s, 1H), 8.32 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.51 (s, 1H), 7.46 (s, 1H), 7.03-6.93 (m, 2H), 6.71-6.68 (m, 1H), 6.65-6.62 (m, 1H), 6.02 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.79-4.68 (m, 2H), 3.15 (br s, 4H), 2.72 (br s, 4H), 2.42 (s, 3H), 1.57 (d, J = 6.4 Hz, 3H).
64 (4 th eluting isomer)	++++					4 th : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.03-6.93 (m, 2H), 6.71-6.68 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.07 (br s, 4H), 2.50-2.48 (m, 4H), 2.26 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
65 (1 st eluting isomer)	++++	2-1, 22-2, 3-7, 36-1	F	(S)-[(1R)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol; (R)-[(1S)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol;	564.0	1 st : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.10-7.05 (m, 1H), 6.99 (s, 1H), 6.76-6.72 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.07 (br

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				(S)-[(1R)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol;		s, 4H), 2.43-2.41 (m, 4H), 2.21 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
66 (2 nd eluting isomer)	++++			(S)-[(3R)-2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-3-methyl-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl][3-(4-methylpiperazin-1-yl)phenyl]methanol		2 nd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.52 (s, 1H), 7.47 (s, 1H), 7.10-7.05 (m, 1H), 6.99 (s, 1H), 6.76-6.72 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.07-3.05 (m, 4H), 2.43-2.41 (m, 4H), 2.21 (s, 3H), 1.58 (d, J = 6.4 Hz, 3H).
67 (3 rd eluting isomer)	++++					3 rd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.52 (s, 1H), 7.47 (s, 1H), 7.10-7.05 (m, 1H), 6.99 (s, 1H), 6.76-6.72 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.08 (br s, 4H), 2.50-2.48 (m, 4H), 2.24 (s, 3H), 1.54 (d, J = 6.4 Hz, 3H).
68 (4 th eluting isomer)	++++					4 th : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.33 (s, 1H), 8.18 (t, J = 8.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.84-7.82 (m, 1H), 7.52 (s, 1H), 7.44 (s, 1H), 7.10-7.05 (m, 1H), 6.99 (s, 1H), 6.76-6.72 (m, 1H), 6.65-6.62 (m, 1H), 6.00 (d, J = 4.0 Hz, 1H), 5.59 (d, J = 4.0 Hz, 1H), 5.07-5.03 (m, 1H), 4.77-4.74 (m, 1H), 4.68-4.64 (m, 1H), 3.08 (br s, 4H), 2.44-2.41 (m, 4H), 2.21 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H).
69 (1 st eluting isomer)	++++	2-1, 12-1, 3-8, 4-14	F	(S)-{3-[(3aR,6aS)-5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl]phenyl}{[2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-	576.0	1 st : (CD ₃ OD, 400 MHz) δ (ppm): 8.35-8.33 (m, 1H), 8.26-8.22 (m, 1H), 8.14-8.12 (m, 1H), 7.87-7.84 (m, 2H), 7.52 (s, 1H), 7.42 (s, 1H),

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol; (R)-{3-[(3aR,6aS)-5-methyloctahydropyrrolo[3,4-c]pyrrol-2-yl]phenyl}({2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		7.10-7.06 (m, 1H), 6.78-6.76 (m, 1H), 6.69-6.67 (m, 1H), 6.58-6.56 (m, 1H), 5.71 (s, 1H), 4.74-4.72(m, 4H), 3.24-3.14 (m, 4H), 2.95-2.93 (m, 4H), 2.40-2.29 (m, 5H).
70 (2 nd eluting isomer)	++++					2 nd (CD ₃ OD, 400 MHz) δ (ppm): 8.35-8.33 (m, 1H), 8.26-8.22 (m, 1H), 8.14-8.12 (m, 1H), 7.87-7.84 (m, 2H), 7.52 (s, 1H), 7.42 (s, 1H), 7.10-7.06 (m, 1H), 6.77-6.76 (m, 1H), 6.70-6.67 (m, 1H), 6.58-6.56 (m, 1H), 5.71 (s, 1H), 4.74-4.68(m, 4H), 3.25-3.17 (m, 4H), 2.96-2.94 (m, 4H), 2.41-2.31 (m, 5H).
71 (1 st eluting isomer)	++++	2-1, 4-15, 37-1, 8-22	L	(S)-{2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}({3-[(1-methylazetidin-3-yl)oxy]phenyl})methanol;	537.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.38 (s, 1H), 8.34 (s, 1H), 8.24-8.20 (m, 1H), 7.90-7.83 (m, 2H), 7.53 (s, 1H), 7.47 (s, 1H), 7.14-7.10 (m, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.81 (s, 1H), 6.60-6.57 (m, 1H), 6.10 (d, J = 4.0 Hz, 1H), 5.63 (d, J = 4.4 Hz, 1H), 4.70-4.63 (m, 5H), 3.71-3.68 (m, 2H), 2.92-2.89 (m, 2H), 2.27 (s, 3H).
72 (2 nd eluting isomer)	++++			(R)-{2-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl}({3-[(1-methylazetidin-3-yl)oxy]phenyl})methanol		
73 (1 st eluting isomer)	++++	38-1, 8-11, 3-9, 4-16	L	(S)-(3-{5-methyl-1H,2H,3H,4H,5H,6H-pyrrolo[3,4-c]pyrrol-2-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	556.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.31(d, J = 4.0 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.45 (s, 2H), 7.00 (t, J = 8.0 Hz, 1H), 6.54-6.49 (m, 2H), 6.29 (d, J = 7.2 Hz, 1H), 5.95 (s, 1H), 5.56 (s, 1H), 4.64-4.62 (m, 4H), 3.92 (s, 4H), 3.46 (s, 4H), 2.46 (s, 3H).
74 (2 nd eluting isomer)	++++			(R)-(3-{5-methyl-1H,2H,3H,4H,5H,6H-pyrrolo[3,4-c]pyrrol-2-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		
75 (2 nd eluting isomer)	++++	8-11	J	(S)-{3-[3-(dimethylamino)azetidin-1-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol; or (R)-{3-[3-(dimethylamino)azetidin-1-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-	532.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47-7.44 (m, 2H), 6.99 (t, J = 8.0 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 6.46 (s, 1H), 6.263-6.20 (m, 1H), 5.97 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 4.0 Hz, 1H), 4.65-4.58 (m, 4H), 3.85-3.82 (m,

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		2H), 3.48-3.40 (m, 2H), 3.11-3.09 (m, 1H), 2.08 (s, 6H).
76 (1 st eluting isomer)	++++	22-1, 23-1, 8-17	J	1-{3-[(R)-methoxy({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methyl}phenyl)-N,N-dimethylazetidin-3-amine;	546.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.33 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 0.8 Hz, 1H), 7.41 (s, 1H), 7.02 (t, J = 8.0 Hz, 1H), 6.54 (d, J = 7.6 Hz, 1H), 6.40 (s, 1H), 6.26-6.23 (m, 1H), 5.20 (s, 1H), 4.70-4.58 (m, 4H), 3.86-3.81 (m, 2H), 3.48-3.43 (m, 2H), 3.22 (s, 3H), 3.14-3.10 (m, 1H), 2.08 (s, 6H).
77 (2 nd eluting isomer)	++++			1-{3-[(S)-methoxy({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methyl}phenyl)-N,N-dimethylazetidin-3-amine		
78 (1 st eluting isomer)	++++	24-2, 26-1	C	(S)-{3-[(1-methylpiperidin-4-yl)oxy]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol;	547.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.35-8.31 (m, 2H), 8.19-8.13 (m, 2H), 8.04-7.98 (m, 2H), 7.50-7.45 (m, 2H), 7.12-7.09 (m, 1H), 6.90-6.89 (m, 1H), 6.83-6.81 (m, 1H), 6.75-6.72 (m, 1H), 6.07-6.06 (m, 1H), 5.62-5.61 (m, 1H), 4.68-4.56 (m, 4H), 4.29-4.25 (m, 1H), 2.60-2.53 (m, 2H), 2.16-2.09 (m, 5H), 1.88-1.84 (m, 2H), 1.62-1.51 (m, 2H).
79 (2 nd eluting isomer)	++++			(R)-{3-[(1-methylpiperidin-4-yl)oxy]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		
80 (1 st eluting isomer)	++			6-[(S)-hydroxy(phenyl)methyl]-2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-5-ium-5-olate;	450.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.36 (s, 1H), 8.18-8.13 (m, 3H), 8.02-7.99 (m, 2H), 7.63 (s, 1H), 7.49 (s, 1H), 7.28-7.16 (m, 5H), 6.97 (s, 1H), 4.69-4.56 (m, 4H).
81 (2 nd eluting isomer)	++			6-[(R)-hydroxy(phenyl)methyl]-2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-5-ium-5-olate		
82 (1 st eluting isomer)	++++	28-1	F	(S)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol;	565.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.38 (s, 1H), 8.24-8.20 (m, 1H), 7.97-7.94 (m, 1H), 7.89-7.87 (m, 1H), 7.53 (s, 1H), 7.06-7.02 (m, 2H), 6.74-6.72 (m, 2H), 5.79-5.78 (m, 1H), 5.61-5.60 (m, 1H), 4.73-4.70 (m, 2H), 4.69-4.65 (m, 2H), 3.10-3.07 (m, 4H), 2.50-2.45 (m, 4H), 2.37-2.33 (m, 3H), 2.25-2.23 (m, 3H).
83 (2 nd eluting isomer)	+++			(R)-{6-[3-fluoro-4-(1,3-oxazol-2-yl)benzenesulfonyl]-4-methyl-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol		

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
84 (1 st eluting isomer)	++++	8-11	J	(S)-(3-{6-methyl-2,6-diazaspiro[3.3]heptan-2-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	544.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.47-7.44 (m, 2H), 7.00-6.96 (m, 1H), 6.58 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 6.20 (d, J = 8.4 Hz, 1H), 5.96 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 3.6 Hz, 1H), 4.64-4.58 (m, 4H), 3.78 (s, 4H), 3.33-3.27 (m, 4H), 2.20 (s, 3H).
85 (2 nd eluting isomer)	++++			(R)-(3-{6-methyl-2,6-diazaspiro[3.3]heptan-2-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		
86 (1 st eluting isomer)	++++	8-11	B	(S)-{3-[(4aS,7aS)-octahydropyrrolo[3,4-b]morpholin-6-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	560.0	1 st : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32-8.30 (m, 2H), 8.21-8.15 (m, 2H), 8.02-7.98 (m, 2H), 7.48-7.44 (m, 2H), 7.02-6.98 (m, 1H), 6.57-6.51 (m, 2H), 6.33 (t, J = 8.4 Hz, 1H), 5.96-5.92 (m, 1H), 5.59-5.55 (m, 1H), 4.63-4.58 (m, 4H), 4.10-3.82 (m, 2H), 3.70-3.45 (m, 3H), 3.20-2.99 (m, 4H), 2.35-2.30 (m, 1H), 2.17-2.12 (m, 1H).
87 (2 nd eluting isomer)	++++			(R)-{3-[(4aS,7aS)-octahydropyrrolo[3,4-b]morpholin-6-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;		2 nd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.8 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 4.0 Hz, 2H), 7.00 (t, J = 8.0 Hz, 1H), 6.55-6.51 (m, 2H), 6.30 (d, J = 8.0 Hz, 1H), 5.95 (d, J = 4.0 Hz, 1H), 5.58 (d, J = 4.0 Hz, 1H), 4.68-4.61 (m, 4H), 3.95-3.91 (m, 1H), 3.70-3.61 (m, 2H), 3.48-3.42 (m, 2H), 3.05-2.91 (m, 5H).
88 (3 rd eluting isomer)	++++			(S)-{3-[(4aR,7aR)-octahydropyrrolo[3,4-b]morpholin-6-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;		3 rd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32-8.31 (m, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.04-7.96 (m, 2H), 7.49-7.44 (m, 2H), 6.99 (t, J = 8.0 Hz, 1H), 6.57-6.50 (m, 2H), 6.32-6.28 (m, 1H), 5.95 (d, J = 4.4 Hz, 1H), 5.58 (d, J = 4.4 Hz, 1H), 4.62-4.57 (m, 4H), 3.96-3.93 (m, 1H), 3.65-3.53 (m, 3H), 3.46-3.40 (m, 1H), 3.08-3.02 (m, 3H), 2.93-2.85 (m, 2H), 2.35-2.30 (m, 1H), 2.15-2.10 (m, 1H).
89	++++			(R)-{3-[(4aR,7aR)-octahydropyrrolo[3,4-b]morpholin-6-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		4 th : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (d, J = 6.4 Hz, 2H), 8.17-8.15 (m, 2H),

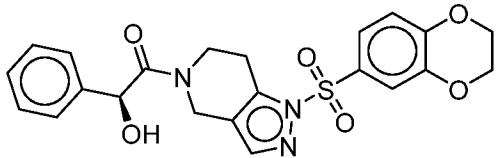
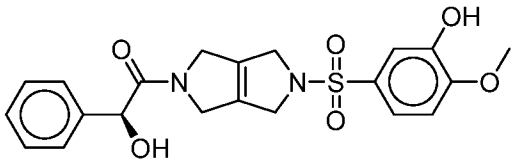
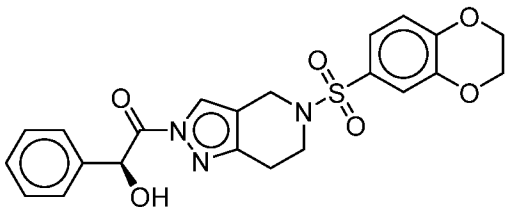
Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
(4 th eluting isomer)						8.02-7.98 (m, 2H), 7.46 (d, J = 6.0 Hz, 2H), 7.01-6.98 (m, 1H), 6.59-6.48 (m, 2H), 6.32-6.30 (m, 1H), 5.97-5.94 (m, 1H), 5.58-5.56 (m, 1H), 4.64-4.62 (m, 4H), 4.04-3.95 (m, 1H), 3.85-3.44 (m, 4H), 3.30-3.28 (m, 1H), 3.08-3.03 (m, 4H).
90 (1 st eluting isomer)	+++			(S)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl](2-{[5-(1,3-oxazol-2-yl)thiophen-2-yl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol;	552.0	(Methanol-d ₄ , 400 MHz) δ (ppm): 8.38 (s, 1H), 8.01-8.00 (m, 1H), 7.73-7.72 (m, 2H), 7.56 (s, 1H), 7.32-7.30 (m, 1H), 7.14-7.12 (m, 1H), 7.09-7.08 (m, 1H), 6.95-6.92 (m, 1H), 5.74 (s, 1H), 4.76 (s, 4H), 3.00 (s, 8H), 2.63 (s, 3H), 2.15 (s, 3H).
91 (2 nd eluting isomer)	++++			(R)-[4-methyl-3-(4-methylpiperazin-1-yl)phenyl](2-{[5-(1,3-oxazol-2-yl)thiophen-2-yl]sulfonyl}-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		
92 (1 st eluting isomer)	++++	8-11	B	(S)-{3-[(3aR,6aR)-octahydropyrrolo[3,4-b]pyrrol-5-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	544.0	1 st : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 6.8 Hz, 2H), 7.03-6.99 (m, 1H), 6.62-6.55 (m, 2H), 6.43-6.41 (m, 1H), 5.98-5.97 (m, 1H), 5.58-5.57 (m, 1H), 4.69-4.62 (m, 4H), 4.00-3.95 (m, 1H), 3.32-3.29 (m, 4H), 3.10-3.07 (m, 1H), 3.00-2.97 (m, 3H), 1.98-1.94 (m, 1H), 1.70-1.68 (m, 1H).
93 (2 nd eluting isomer)	++++			(R)-{3-[(3aR,6aR)-octahydropyrrolo[3,4-b]pyrrol-5-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;		2 nd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 4.8 Hz, 2H), 7.03-6.98 (m, 1H), 6.64-6.62 (m, 1H), 6.58-6.55 (m, 1H), 6.43-6.40 (m, 1H), 5.99-5.97 (m, 1H), 5.58-5.56 (m, 1H), 4.69-4.63 (m, 4H), 3.99-3.94 (m, 1H), 3.31-3.28 (m, 4H), 3.09-3.06 (m, 1H), 3.00-2.95 (m, 3H), 2.00-1.95 (m, 1H), 1.69-1.67 (m, 1H).
94 (3 rd eluting isomer)	++++			(S)-{3-[(3aS,6aS)-octahydropyrrolo[3,4-b]pyrrol-5-yl]phenyl}({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		3 rd : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 7.2 Hz, 2H), 7.00-6.98 (m, 1H), 6.63-6.61 (m, 1H), 6.58-6.56

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
						(m, 1H), 6.40-6.37 (m, 1H), 5.94 (d, J = 4.0 Hz, 1H), 5.56 (d, J = 4.0 Hz, 1H), 4.68-4.63 (m, 4H), 3.85-3.81 (m, 1H), 3.31-3.26 (m, 3H), 3.04-3.02 (m, 1H), 2.98-2.95 (m, 1H), 2.81-2.74 (m, 3H), 2.00-1.95 (m, 1H), 1.69-1.67 (m, 1H).
95 (4 th eluting isomer)	++++					4 th : (DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 5.2 Hz, 2H), 7.01-6.96 (m, 1H), 6.63-6.61 (m, 1H), 6.58-6.56 (m, 1H), 6.40-6.37 (m, 1H), 5.95 (d, J = 3.6 Hz, 1H), 5.56 (d, J = 3.6 Hz, 1H), 4.69-4.63 (m, 4H), 4.00-3.95 (m, 1H), 3.30-3.26 (m, 3H), 3.05-3.03 (m, 1H), 2.97-2.94 (m, 1H), 2.80-2.73 (m, 3H), 2.00-1.95 (m, 1H), 1.69-1.67 (m, 1H).
96 (1 st eluting isomer)	++++	4-13, 8-11	B	(S)-(3-{3,6-diazabicyclo[3.1.1]heptan-3-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol;	530.0	(CD ₃ OD, 400 MHz) δ (ppm): 8.31 (s, 1H), 8.21 (d, J = 8.8 Hz, 2H), 8.07-8.03 (m, 3H), 7.53 (s, 1H), 7.38 (s, 1H), 7.16-7.12 (m, 1H), 6.84 (s, 1H), 6.70-6.63 (m, 2H), 5.74 (s, 1H), 4.72 (s, 4H), 4.02-3.99 (m, 2H), 3.65-3.55 (m, 4H), 2.82-2.80 (m, 1H), 1.75-1.73 (m, 1H).
97 (2 nd eluting isomer)	++++			(R)-(3-{3,6-diazabicyclo[3.1.1]heptan-3-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl})methanol		
98 (1 st eluting isomer)	++++	4-5, 25-2, 27-1, 3-2, 33-1	F	(S)-[3-(4-methylpiperazin-1-yl)phenyl]({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol;	533.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.64 (s, 1H), 8.33 (s, 1H), 8.15 (d, J = 8.4 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.06-7.02 (m, 2H), 6.74-6.71 (m, 2H), 5.87 (d, J = 6.0 Hz, 1H), 5.64 (d, J = 5.6 Hz, 1H), 4.67-4.63 (m, 4H), 3.07-3.05 (m, 4H), 2.42-2.40 (m, 4H), 2.21 (s, 3H).
99 (2 nd eluting isomer)	++++			(R)-[3-(4-methylpiperazin-1-yl)phenyl]({6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl})methanol		
100 (1 st eluting isomer)	++++	4-13, 8-11	J	(S)-(3-{5-methyloctahydropyrrolo[3,4-c]pyrrol-2-yl}phenyl)({2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-	558.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 2H), 8.16 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 5.6 Hz, 2H), 6.99-6.97 (m, 1H),

Cmpd. No.	IC ₅₀ (μM)	Inter-mediates	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
101 (2 nd eluting isomer)	++++			1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol; (R)-(3-{5-methyl-octahydropyrrolo[3,4-c]pyrrol-2-yl}phenyl){2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		6.65-6.63 (m, 1H), 6.57-6.55 (m, 1H), 6.43-6.42 (m, 1H), 5.95 (d, J = 4.0 Hz, 1H), 5.57 (d, J = 4.0 Hz, 1H), 4.65-4.62 (m, 4H), 3.29-3.26 (m, 2H), 3.01-2.99 (m, 2H), 2.84 (s, 2H), 2.55-2.52 (m, 2H), 2.39-2.37 (m, 2H), 2.21 (s, 3H).
102 (1 st eluting isomer)	++++	24-1, 3-4, 4-4, 25-1	F	(S)-[2-(4-methylpiperazin-1-yl)phenyl]{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol;	532.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.33 (s, 1H), 8.29 (s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.52-7.46 (m, 2H), 7.18-7.08 (m, 3H), 6.97-6.93 (m, 1H), 6.12 (d, J = 4.8 Hz, 1H), 5.90 (d, J = 5.2 Hz, 1H), 4.72-4.61 (m, 4H), 2.87-2.85 (m, 4H), 2.37 (s, 4H), 2.18 (s, 3H).
103 (2 nd eluting isomer)	++++			(R)-[2-(4-methylpiperazin-1-yl)phenyl]{2-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-6-yl)methanol		
104 (1 st eluting isomer)	--			N-[4-({6-[(S)-hydroxy[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)phenyl]cyclopropa ncarboxamide;	562.0	(CD ₃ OD-d ₄ , 400 MHz) δ (ppm): 8.31 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 2.1 Hz, 1H), 7.49 (d, J = 8.8 Hz, 1H), 7.45 (s, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.07 (d, J = 7.9 Hz, 2H), 5.99 (d, J = 4.2 Hz, 1H), 5.63 (d, J = 4.0 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.77-4.66 (m, 2H), 4.62 (d, J = 14.3 Hz, 1H), 2.78 (s, 4H), 2.75-2.69 (m, 3H), 2.26 (d, J = 14.3 Hz, 6H), 1.83-1.72 (m, 1H), 1.24 (s, 1H), 0.88-0.79 (m, 4H).
105 (2 nd eluting isomer)	+++			N-[4-({6-[(R)-hydroxy[4-methyl-3-(4-methylpiperazin-1-yl)phenyl]methyl]-1H,2H,3H-pyrrolo[3,4-c]pyridin-2-yl}sulfonyl)phenyl]cyclopropa ncarboxamide		
106 (1 st eluting isomer)	++++	29-1	F	(S)-{4-methoxy-6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol;	563.0	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.32 (s, 1H), 8.16 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 7.07-7.04 (m, 2H), 6.80-6.78 (m, 2H), 5.77 (d, J = 6.0 Hz, 1H), 5.53 (d, J = 6.0 Hz, 1H), 4.62-4.52 (m, 4H), 3.95 (s, 3H), 3.08-3.06 (m, 4H), 2.44 (s, 4H), 2.21 (s, 3H).
107 (2 nd eluting isomer)	++++			(R)-{4-methoxy-6-[4-(1,3-oxazol-2-yl)benzenesulfonyl]-5H,6H,7H-pyrrolo[3,4-d]pyrimidin-2-yl}[3-(4-methylpiperazin-1-yl)phenyl]methanol		
108 (1 st eluting isomer)	++++			(S)-(3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)(2-(naphthalen-2-ylsulfonyl)-2,3-dihydro-1H-	527.2	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.55 (s, 1H), 8.30 (s, 1H), 8.20 (d, 1H), 8.11 (d, 1H), 8.03 (dd, 1H), 7.87 (dd, 1H), 7.73-7.65 (m, 2H), 7.42

Cmpd. No.	IC ₅₀ (μM)	Inter-mediate	Synth. Method	Chemical Name	MS m/z [M+H] ⁺	¹ H NMR
				pyrrolo[3,4-c]pyridin-6-yl)methanol		(s, 1H), 6.98 (t, 1H), 6.58-6.56 (m, 1H), 6.42 (s, 1H), 6.22-6.19 (m, 1H), 5.92 (d, 1H), 5.54 (d, 1H), 4.68-4.64 (m, 4H), 3.80-3.76 (m, 4H), 3.31 (s, 4H), 2.25 (s, 3H).
109 (2 nd eluting isomer)	++++			(R)-(3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)(2-(naphthalen-2-ylsulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)methanol	527.2	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.55 (s, 1H), 8.30 (s, 1H), 8.20 (d, 1H), 8.11 (d, 1H), 8.03 (dd, 1H), 7.87 (dd, 1H), 7.73-7.66 (m, 2H), 7.42 (s, 1H), 6.99 (t, 1H), 6.58-6.56 (m, 1H), 6.42 (s, 1H), 6.22-6.19 (m, 1H), 5.92 (d, 1H), 5.54 (d, 1H), 4.68-4.64 (m, 4H), 3.80-3.76 (m, 4H), 3.32 (s, 4H), 2.25 (s, 3H).
110	+++			(S)-(2-((6-methoxynaphthalen-2-yl)sulfonyl)-2,3-dihydro-1H-pyrrolo[3,4-c]pyridin-6-yl)(3-(6-methyl-2,6-diazaspiro[3.3]heptan-2-yl)phenyl)methanol	557.3	(DMSO-d ₆ , 400 MHz) δ (ppm): 8.45 (s, 1H), 8.30 (s, 1H), 8.10 (d, 1H), 7.97 (d, 1H), 7.83-7.80 (m, 1H), 7.44-7.42 (m, 1H), 7.32-7.29 (m, 2H), 6.99 (t, 1H), 6.58-6.56 (m, 1H), 6.42 (s, 1H), 6.22-6.19 (m, 1H), 5.92 (d, 1H), 5.53 (d, 1H), 4.65-4.58 (m, 4H), 3.90 (s, 3H), 3.80-3.76 (m, 4H), 3.32 (s, 4H), 2.23 (s, 3H).

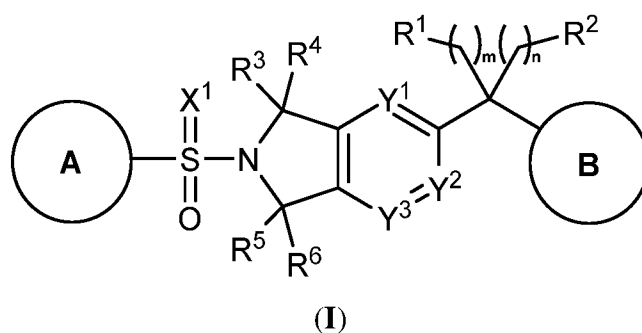
Table 17. Biological Data of Additional Compounds

Cmpd. No.	Structure	IC ₅₀ (μM)
A-1		--
A-2		--
A-3		--

Cmpd. No.	Structure	IC ₅₀ (μM)
A-4		--
A-5		--
A-6		--
A-7		--

Embodiments

[0265] Embodiment 1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X¹ is NR or O;

Y¹ is CR⁷ or N;

Y² is CR⁸ or N;

Y³ is CR⁹ or N;

wherein the heteroaryl formed when at least one of Y¹, Y², or Y³ is N may comprise an N-oxide;

Ring A is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring A is optionally substituted with one or more R^a;

each R^a is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R^a group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

Ring B is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring B is optionally substituted with one or more R^b;

each R^b is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R^b group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R¹ and R² are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from

N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

or R¹ and R² combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R¹ and R² group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₈cycloalkyl, and optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S

or R³ and R⁴, or R⁵ and R⁶, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R³, R⁴, R⁵, and R⁶ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆ aliphatic;

R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, and optionally substituted C₁-C₆aliphatic,

wherein an optionally substituted R⁷, R⁸, and R⁹ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R group may be optionally substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

each R' is independently selected from the group consisting of optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R' group may be substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

m is 0, 1, or 2; and

n is 0, 1, or 2.

[0266] Embodiment 2. The compound of embodiment 1, wherein:

Ring A is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a; or

(ii) a bicyclic 6- to 12-membered ring comprising a C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,

wherein the C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^a; and

Ring B is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^b ; or

(ii) a bicyclic 6- to 12-membered ring comprising a C_3 - C_{10} carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,

wherein the C_3 - C_{10} carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^b .

[0267] Embodiment 3. The compound of any one of the preceding claims, wherein:

X^1 is O;

Y^1 is CR^7 or N;

Y^2 is CR^8 or N;

Y^3 is CR^9 or N;

wherein the heteroaryl formed when at least one of Y^1 , Y^2 , or Y^3 is N may comprise an N-oxide;

Ring A is:

(i) a monocyclic ring selected from C_3 - C_8 carbocyclyl, phenyl, or 5- to 8-membered heteroaryl,

wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a ; or

(ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,

wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^a ;

each R^a is independently selected from the group consisting of halogen, -OR, -NRC(O)R', optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

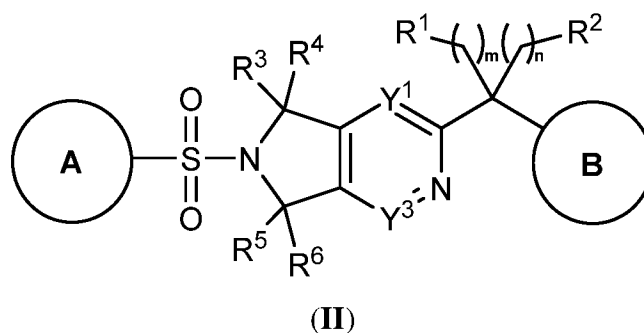
wherein an optionally substituted R^a group may be substituted with one or more halogen;

Ring B is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl ring,
wherein the monocyclic ring is optionally substituted with one or more R^b; or
(ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,
wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and
wherein the bicyclic ring is optionally substituted with one or more R^b;
each R^b is independently selected from the group consisting of halogen, -OR, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,
wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of -NR₂ and C₁-C₆ aliphatic;
R¹ and R² are each independently selected from the group consisting of -H, -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic;
R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H and C₁-C₆aliphatic;
R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, -OR, and C₁-C₆aliphatic;
each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,
wherein an optionally substituted R group may be optionally substituted with one or more C₁-C₆aliphatic;
each R' is independently C₃-C₁₀cycloalkyl;
m is 0, 1, or 2; and
n is 0.

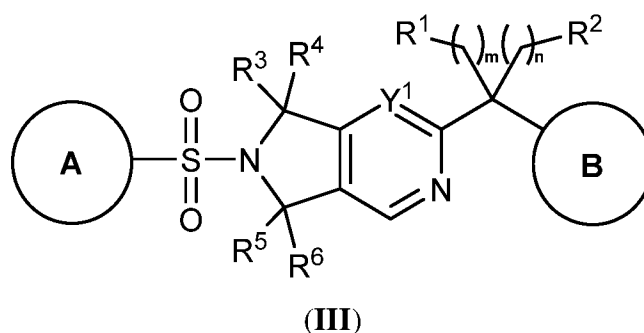
[0268] Embodiment 4. The compound of any one of the preceding embodiments, wherein X¹ is O.

[0269] Embodiment 5. The compound of any one of the preceding embodiments, wherein the compound is of Formula II:



or a pharmaceutically acceptable salt thereof.

[0270] Embodiment 6. The compound of any one of the preceding embodiments, wherein the compound is of Formula III:



or a pharmaceutically acceptable salt thereof.

[0271] Embodiment 7. The compound of any one of the preceding embodiments, wherein R^1 and R^2 are each independently selected from the group consisting of -H, -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic.

[0272] Embodiment 8. The compound of any one of the preceding embodiments, wherein R^1 and R^2 are each independently selected from the group consisting of -H and -OR.

[0273] Embodiment 9. The compound of any one of the preceding embodiments, wherein R^2 is -H.

[0274] Embodiment 10. The compound of any one of the preceding embodiments, wherein R^1 is selected from the group consisting of -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic.

[0275] Embodiment 11. The compound of any one of the preceding embodiments, wherein R^1 is -OH.

[0276] Embodiment 12. The compound of any one of the preceding embodiments, wherein m is 0 or 1.

[0277] Embodiment 13. The compound of any one of the preceding embodiments, wherein m is 0.

[0278] Embodiment 14. The compound of any one of the preceding embodiments, wherein n is 0 or 1.

[0279] Embodiment 15. The compound of any one of the preceding embodiments, wherein n is 0.

[0280] Embodiment 16. The compound of any one of the preceding embodiments, wherein R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of -H and C_1 - C_6 aliphatic.

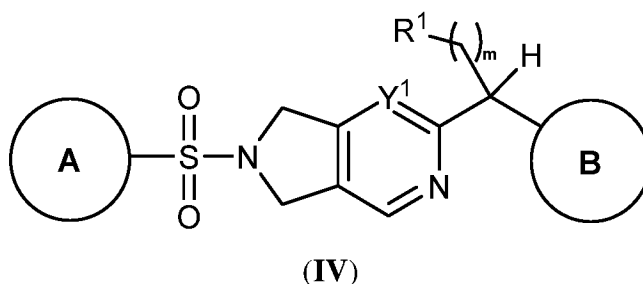
[0281] Embodiment 17. The compound of any one of the preceding embodiments, wherein R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of -H and methyl.

[0282] Embodiment 18. The compound of any one of the preceding embodiments, wherein R^3 is methyl, and R^4 , R^5 , and R^6 are each -H.

[0283] Embodiment 19. The compound of any one of the preceding embodiments, wherein R^5 is methyl, and R^3 , R^4 , and R^6 are each -H.

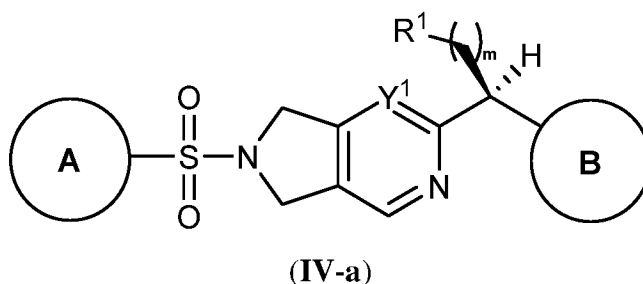
[0284] Embodiment 20. The compound of any one of the preceding embodiments, wherein R^3 , R^4 , R^5 , and R^6 are each -H.

[0285] Embodiment 21. The compound of any one of the preceding embodiments, wherein the compound is of Formula IV:



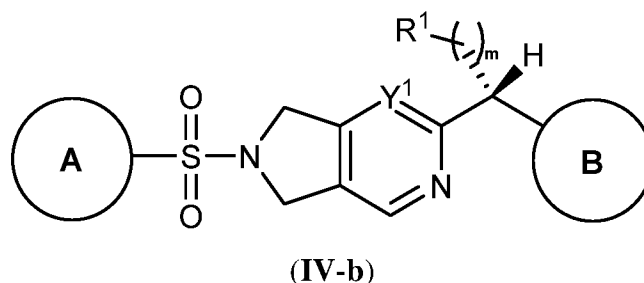
or a pharmaceutically acceptable salt thereof.

[0286] Embodiment 22. The compound of any one of the preceding embodiments, wherein the compound is of Formula IV-a:



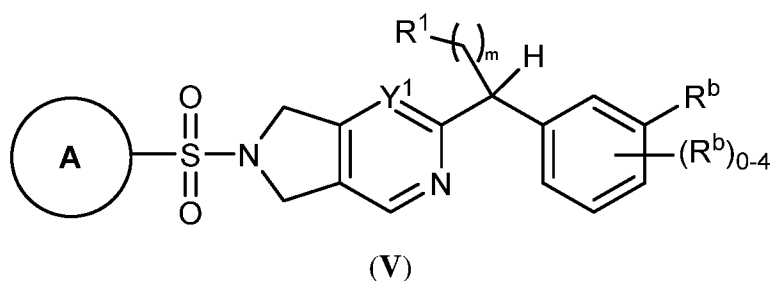
or a pharmaceutically acceptable salt thereof.

[0287] Embodiment 23. The compound of any one of the preceding embodiments, wherein the compound is of Formula IV-b:



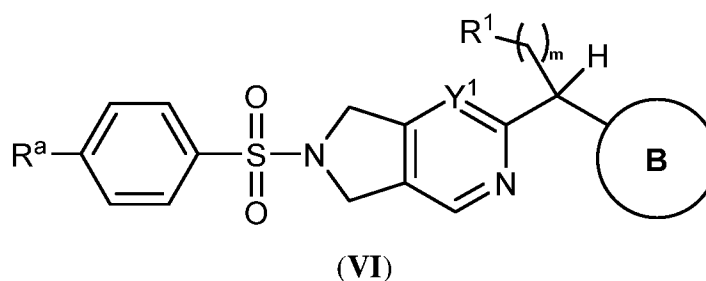
or a pharmaceutically acceptable salt thereof.

[0288] Embodiment 24. The compound of any one of the preceding embodiments, wherein the compound is of Formula V:



or a pharmaceutically acceptable salt thereof.

[0289] Embodiment 25. The compound of any one of the preceding embodiments, wherein the compound is of Formula VI:



or a pharmaceutically acceptable salt thereof.

[0290] Embodiment 26. The compound of any one of the preceding embodiments, wherein Ring A is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl, phenyl, or 5- to 8-membered heteroaryl, wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the monocyclic ring is optionally substituted with one or more R^a; or

(ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,

wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^a.

[0291] Embodiment 27. The compound of any one of the preceding embodiments, wherein Ring A is:

(i) a phenyl ring,

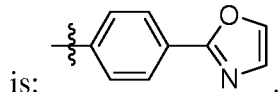
(ii) 5- to 6-membered monocyclic heteroaryl ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S, or

(iii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 6-membered carbocyclic ring or 5- to 6-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein Ring A is optionally substituted with one or more R^a.

[0292] Embodiment 28. The compound of any one of the preceding embodiments, wherein Ring A is phenyl optionally substituted with one or more R^a.

[0293] Embodiment 29. The compound of any one of the preceding embodiments, wherein Ring A



[0294] Embodiment 30. The compound of any one of the preceding embodiments, wherein Ring B is:

(i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl ring,

wherein the monocyclic ring is optionally substituted with one or more R^b; or

(ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,

wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,

wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and

wherein the bicyclic ring is optionally substituted with one or more R^b.

[0295] Embodiment 31. The compound of any one of the preceding embodiments, wherein Ring B is:

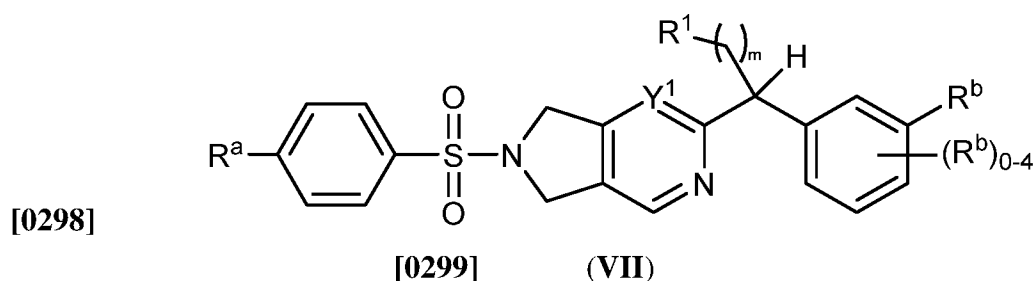
(i) phenyl ring, or

(ii) a 9- to 10-membered bicyclic ring comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 5- to 7-membered carbocyclic ring or 5- to 7-membered heterocyclic ring containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein Ring B is optionally substituted with one or more R^b .

[0296] Embodiment 32. The compound of any one of the preceding embodiments, wherein Ring B is a phenyl ring optionally substituted with one or more R^b .

[0297] Embodiment 33. The compound of any one of the preceding embodiments, wherein the compound is of Formula VII:



or a pharmaceutically acceptable salt thereof.

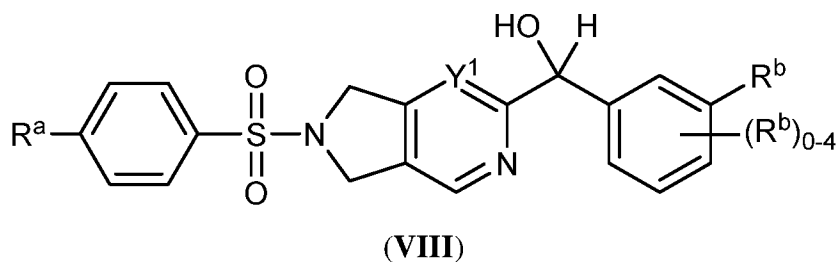
[0300] Embodiment 34. The compound of any one of the preceding embodiments, wherein R^1 is selected from the group consisting of -OR, -NR₂, -CN, -C(O)NR₂, and C₁-C₆aliphatic.

[0301] Embodiment 35. The compound of any one of the preceding embodiments, wherein R^1 is -OH.

[0302] Embodiment 36. The compound of any one of the preceding embodiments, wherein m is 0 or 1.

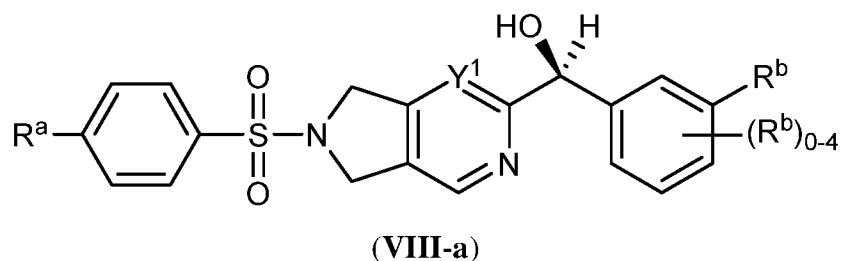
[0303] Embodiment 37. The compound of any one of the preceding embodiments, wherein m is 0.

[0304] Embodiment 38. The compound of any one of the preceding embodiments, wherein the compound is of Formula VIII:



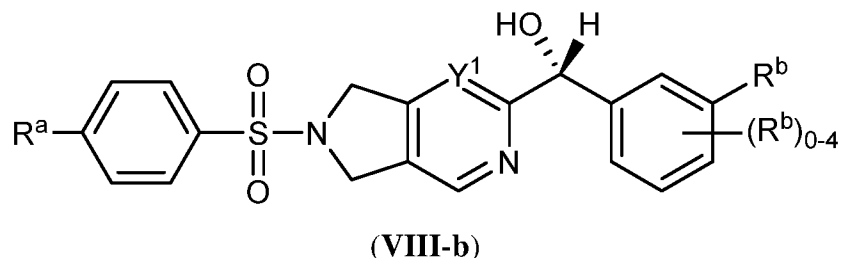
or a pharmaceutically acceptable salt thereof.

[0305] Embodiment 39. The compound of any one of the preceding embodiments, wherein the compound is of Formula VIII-a:



or a pharmaceutically acceptable salt thereof.

[0306] Embodiment 40. The compound of any one of the preceding embodiments, wherein the compound is of Formula VIII-b:



or a pharmaceutically acceptable salt thereof.

[0307] Embodiment 41. The compound of any one of the preceding embodiments, wherein R^7 , R^8 , and R^9 , if present, are each -H, halogen, -OR, -NR₂, -CN, and C₁-C₆aliphatic optionally substituted with halogen.

[0308] Embodiment 42. The compound of any one of the preceding embodiments, wherein R^7 , R^8 , and R^9 , if present, are each independently selected from the group consisting of -H, -OR, and C₁-C₆aliphatic.

[0309] Embodiment 43. The compound of any one of the preceding embodiments, wherein R^7 , R^8 , and R^9 , if present, are each -H.

[0310] Embodiment 44. The compound of any one of the preceding embodiments, wherein Y^1 , Y^2 , and Y^3 are each CH or N.

[0311] Embodiment 45. The compound of any one of the preceding embodiments, wherein Y^1 is CH or N.

[0312] Embodiment 46. The compound of any one of the preceding embodiments, wherein Y^1 is CH.

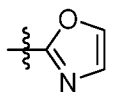
[0313] Embodiment 47. The compound of any one of the preceding embodiments, wherein Y^1 is N.

[0314] Embodiment 48. The compound of any one of the preceding embodiments, wherein each R^a is independently halogen, -OR, -NRC(O)R', optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, or optionally substituted 5- to 10-

membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen.

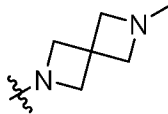
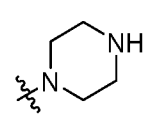
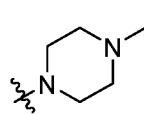
[0315] Embodiment 49. The compound of any one of the preceding embodiments, wherein each R^a is independently halogen or optionally substituted 5-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen.

[0316] Embodiment 50. The compound of any one of the preceding embodiments, wherein R^a is



[0317] Embodiment 51. The compound of any one of the preceding embodiments, wherein each R^b is independently selected from the group consisting of -OR, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of -NR₂ and C₁-C₆ aliphatic.

[0318] Embodiment 52. The compound of any one of the preceding embodiments, wherein each R^b

is independently selected from the group consisting of methyl, , , and .

[0319] Embodiment 53. The compound of any one of the preceding embodiments, wherein each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆ aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R group may be optionally substituted with one or more C₁-C₆ aliphatic.

[0320] Embodiment 54. The compound of any one of the preceding embodiments, wherein each R is -H.

[0321] Embodiment 55. The compound of any one of the preceding embodiments, wherein each R' is independently C₁-C₆ aliphatic or C₃-C₁₀ cycloalkyl.

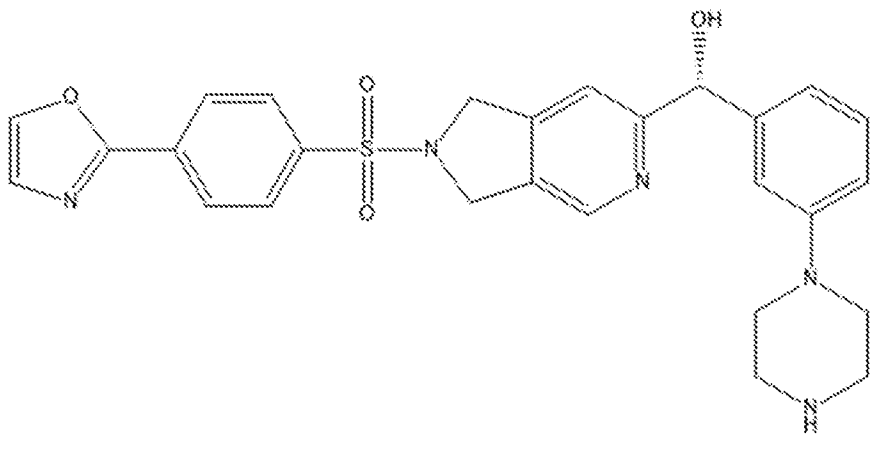
[0322] Embodiment 56. A compound selected from Table 1.

[0323] Embodiment 57. A compound of any one of the preceding embodiments, wherein the compound is a USP9X Inhibitor having an IC₅₀ value ≤ 0.1 μM in the assay of Example 3.

[0324] Embodiment 58. A compound of any one of the preceding embodiments, wherein the compound is a USP9X Inhibitor having an IC₅₀ value ≤ 1 μM in the assay of Example 3.

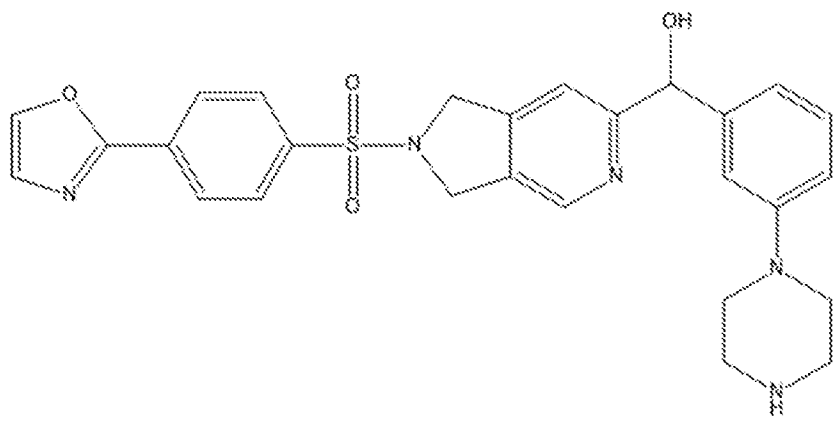
[0325] Embodiment 59. A pharmaceutical composition, comprising a compound of any one of the preceding embodiments, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0326] Embodiment 60. A compound of the formula



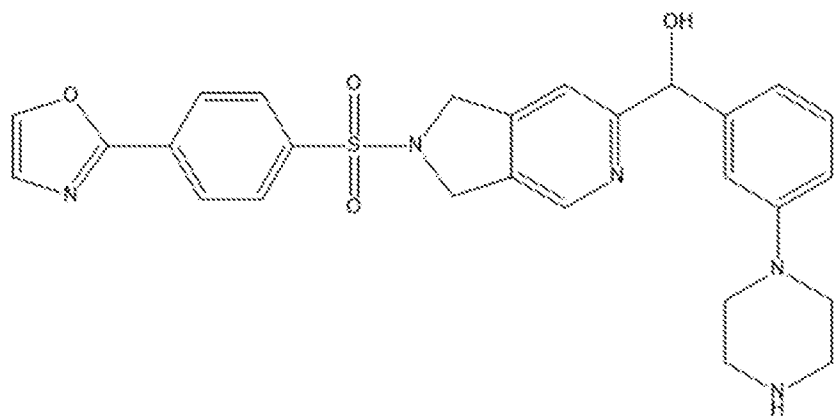
or a pharmaceutically-acceptable salt thereof.

[0327] Embodiment 61. A compound of the formula



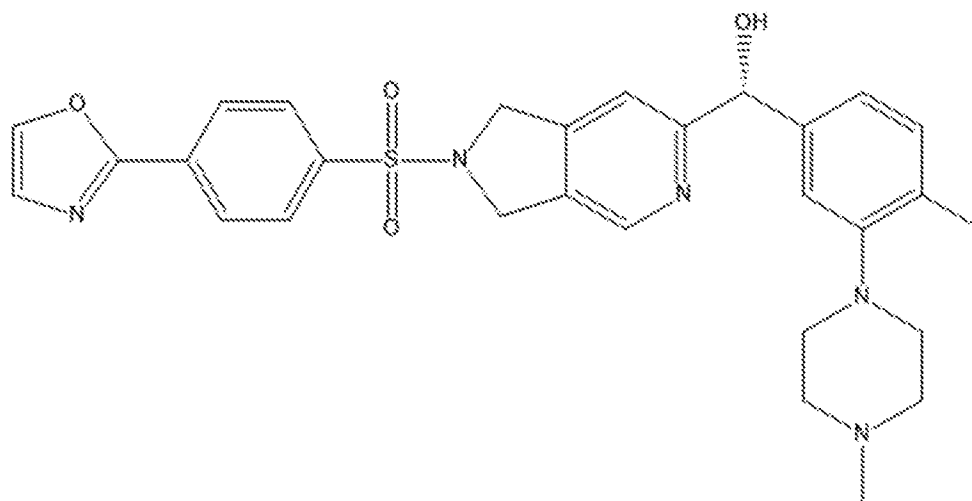
or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the first eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method D-2.

[0328] Embodiment 62. A compound of the formula



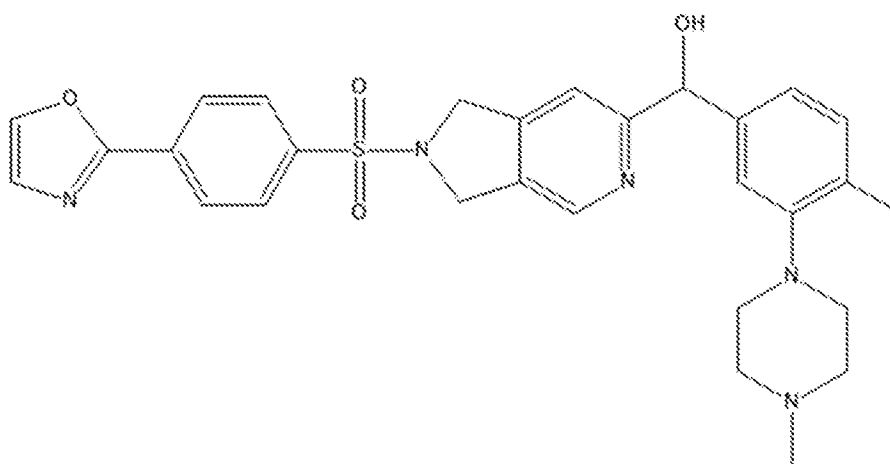
or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the second eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method D-2.

[0329] Embodiment 63. A compound of the formula



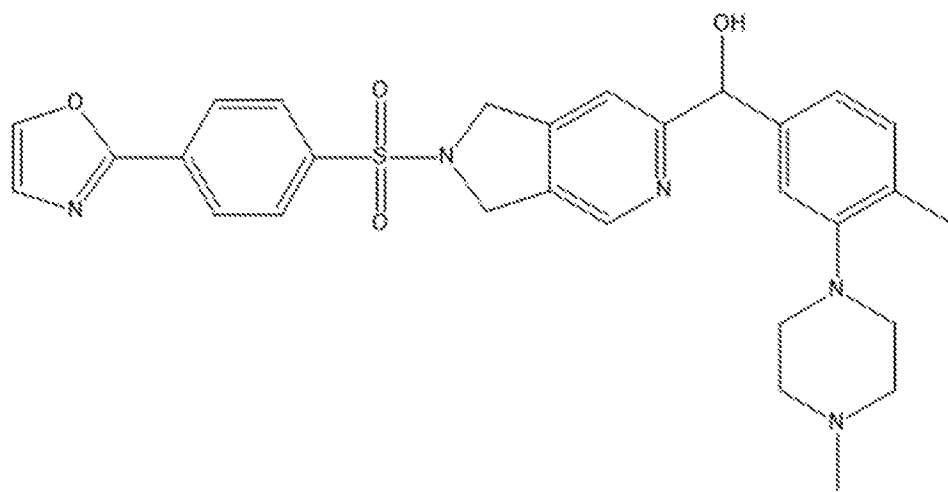
or a pharmaceutically-acceptable salt thereof.

[0330] Embodiment 64. A compound of the formula



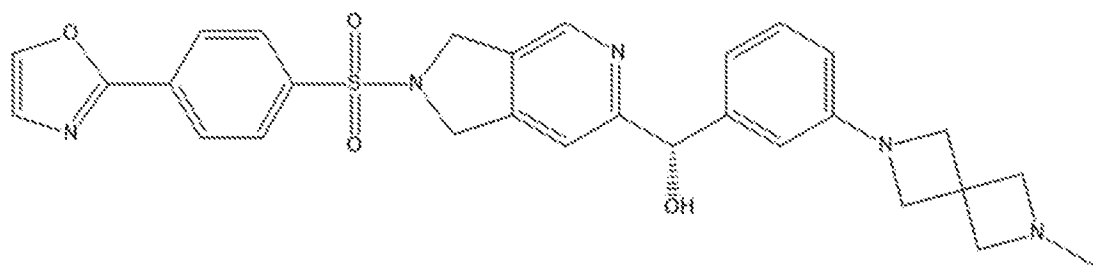
or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the first eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method M.

[0331] Embodiment 65. A compound of the formula



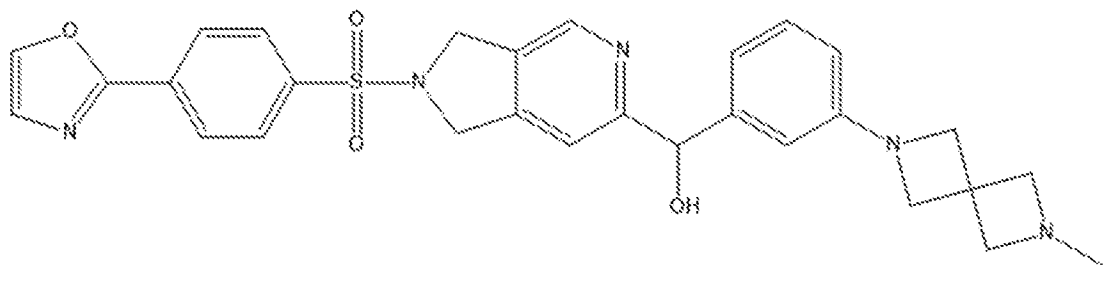
or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the second eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method M

[0332] Embodiment 66. A compound of the formula



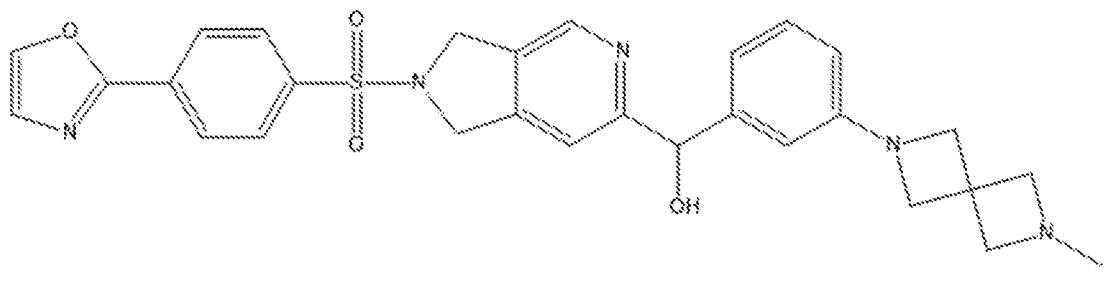
or a pharmaceutically-acceptable salt thereof.

[0333] Embodiment 67. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the first eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method N.

[0334] Embodiment 68. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein the compound has the absolute stereochemistry of the second eluting isomer when a racemic mixture of enantiomers is separated by preparative supercritical fluid chromatography as described in Method N.

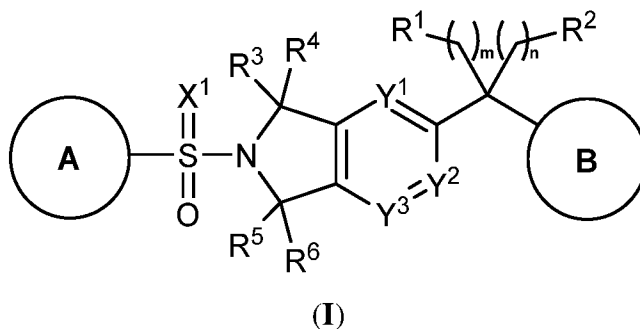
Equivalents

[0335] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

We claim:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is NR or O;

Y^1 is CR^7 or N;

Y^2 is CR^8 or N;

Y^3 is CR^9 or N;

wherein the heteroaryl formed when at least one of Y^1 , Y^2 , or Y^3 is N may comprise an N-oxide;

Ring A is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring A is optionally substituted with one or more R^a ;

each R^a is independently selected from the group consisting of halogen, oxo, -OR, -OC(O) R' , -NR₂,

-NRC(O) R' , -NRS(O)₂ R' , -CN, -NO₂, -SR, -C(O) R' , -C(O)OR, -C(O)NR₂, -S(O)₂ R' ,

-S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl,

optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-

membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R^a group may be substituted with one or more substituents

selected from the group consisting of halogen, oxo, -OR, -OC(O) R' , -NR₂, -NRC(O) R' ,

-NRS(O)₂ R' , -CN, -NO₂, -SR, -C(O) R' , -C(O)OR, -C(O)NR₂, -S(O)₂ R' , -S(O)₂NR₂, and

C₁-C₆aliphatic;

Ring B is a monocyclic or bicyclic 3- to 12-membered ring,

wherein the ring is saturated, fully or partially unsaturated, or aromatic, and

wherein the ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and

wherein Ring B is optionally substituted with one or more R^b;

each R^b is independently selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, optionally substituted C₁-C₆ aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^b group may be substituted with one or more substituents selected from the group consisting of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R¹ and R² are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

or R¹ and R² combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R¹ and R² group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

R³, R⁴, R⁵, and R⁶ are each independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₈cycloalkyl, and optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S

or R³ and R⁴, or R⁵ and R⁶, or a combination thereof, combine with the carbon to which they are attached to form an optionally substituted C₃-C₈cycloalkyl or an optionally substituted 3- to 8-membered heterocyclyl containing 1-4 heteroatoms independently selected from the group consisting of N, O, and S,

wherein an optionally substituted R³, R⁴, R⁵, and R⁶ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆ aliphatic;

R⁷, R⁸, and R⁹ are each independently selected from the group consisting of -H, halogen, -OR, -OC(O)R', -OS(O)₂R', -OS(O)₂NR₂, -OC(O)NR₂, -OC(O)OR, -NR₂, -NRC(O)R', -NRS(O)₂R', -NRC(O)NR₂, -NRC(O)OR, -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -SO₂NR₂, -S(O)₂OR, and optionally substituted C₁-C₆aliphatic,

wherein an optionally substituted R⁷, R⁸, and R⁹ group may be substituted with one or more of halogen, oxo, -OR, -OC(O)R', -NR₂, -NRC(O)R', -NRS(O)₂R', -CN, -NO₂, -SR, -C(O)R', -C(O)OR, -C(O)NR₂, -S(O)₂R', -S(O)₂NR₂, and C₁-C₆aliphatic;

each R is independently selected from the group consisting of -H, optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R group may be optionally substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

each R' is independently selected from the group consisting of optionally substituted C₁-C₆aliphatic, optionally substituted C₃-C₁₀cycloalkyl, optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, optionally substituted phenyl, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S,

wherein an optionally substituted R' group may be substituted with one or more of halogen, oxo, -OH, -O(C₁-C₆aliphatic), -NH₂, -NH(C₁-C₆aliphatic), -N(C₁-C₆aliphatic)₂, -CN, and C₁-C₆aliphatic;

m is 0, 1, or 2; and

n is 0, 1, or 2.

2. The compound of claim 1, wherein:

Ring A is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,
wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and
wherein the monocyclic ring is optionally substituted with one or more R^a; or
- (ii) a bicyclic 6- to 12-membered ring comprising a C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,
wherein the C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and
wherein the bicyclic ring is optionally substituted with one or more R^a; and

Ring B is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl, 3- to 8-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl,
wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and
wherein the monocyclic ring is optionally substituted with one or more R^b; or
- (ii) a bicyclic 6- to 12-membered ring comprising a C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring,
wherein the C₃-C₁₀carbocyclyl, 3- to 10-membered heterocyclyl, phenyl, or 5- to 8-membered heteroaryl ring is fused to an aromatic, saturated, or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of N, O, and S, and
wherein the bicyclic ring is optionally substituted with one or more R^b.

3. The compound of any one of the preceding claims, wherein:

X¹ is O;

Y¹ is CR⁷ or N;

Y² is CR⁸ or N;

Y³ is CR⁹ or N;

wherein the heteroaryl formed when at least one of Y¹, Y², or Y³ is N may comprise an N-oxide;

Ring A is:

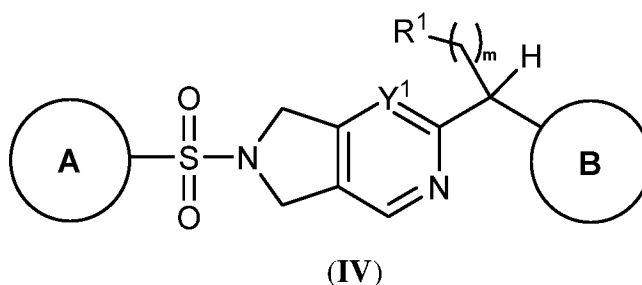
- (i) a monocyclic ring selected from C₃-C₈carbocyclyl, phenyl, or 5- to 8-membered heteroaryl, wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and wherein the monocyclic ring is optionally substituted with one or more R^a; or
- (ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring, wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and wherein the bicyclic ring is optionally substituted with one or more R^a;
- each R^a is independently selected from the group consisting of halogen, -OR, -NRC(O)R', optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S, and optionally substituted 5- to 10-membered heteroaryl containing 1-4 heteroatoms independently selected from N, O, and S, wherein an optionally substituted R^a group may be substituted with one or more halogen;

Ring B is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl ring, wherein the monocyclic ring is optionally substituted with one or more R^b; or
- (ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring, wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and wherein the bicyclic ring is optionally substituted with one or more R^b;

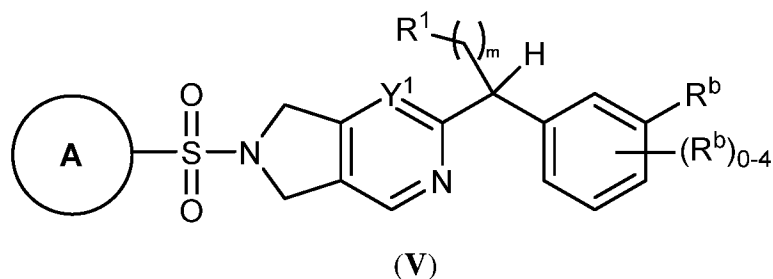
each R^b is independently selected from the group consisting of halogen, -OR, optionally substituted C_1 - C_6 aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,
 wherein an optionally substituted R^b group may be substituted with one or more substituents independently selected from the group consisting of $-NR_2$ and C_1 - C_6 aliphatic;
 R^1 and R^2 are each independently selected from the group consisting of -H, -OR, $-NR_2$, -CN, $-C(O)NR_2$, and C_1 - C_6 aliphatic;
 R^3 , R^4 , R^5 , and R^6 are each independently selected from the group consisting of -H and C_1 - C_6 aliphatic;
 R^7 , R^8 , and R^9 are each independently selected from the group consisting of -H, -OR, and C_1 - C_6 aliphatic;
 each R is independently selected from the group consisting of -H, optionally substituted C_1 - C_6 aliphatic, and optionally substituted 3- to 10-membered heterocyclyl containing 1-4 heteroatoms independently selected from N, O, and S,
 wherein an optionally substituted R group may be optionally substituted with one or more C_1 - C_6 aliphatic;
 each R' is independently C_3 - C_{10} cycloalkyl;
 m is 0, 1, or 2; and
 n is 0.

4. The compound of any one of the preceding claims, wherein the compound is of Formula IV:



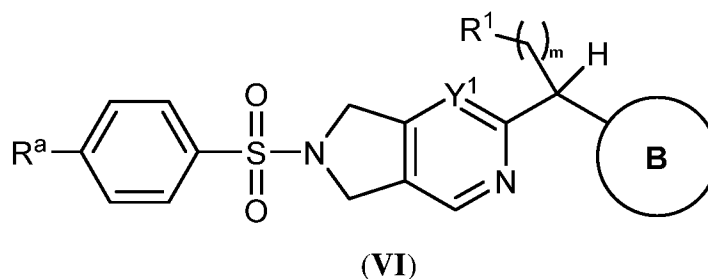
or a pharmaceutically acceptable salt thereof.

5. The compound of any one of the preceding claims, wherein the compound is of Formula V:



or a pharmaceutically acceptable salt thereof.

6. The compound of any one of the preceding claims, wherein the compound is of Formula VI:



or a pharmaceutically acceptable salt thereof.

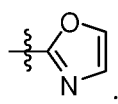
7. The compound of any one of the preceding claims, wherein Ring A is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl, phenyl, or 5- to 8-membered heteroaryl, wherein the monocyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and wherein the monocyclic ring is optionally substituted with one or more R^a; or
- (ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring, wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring, wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and wherein the bicyclic ring is optionally substituted with one or more R^a.

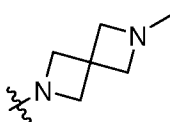
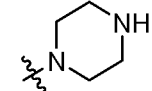
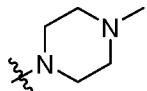
8. The compound of any one of the preceding claims, wherein Ring B is:

- (i) a monocyclic ring selected from C₃-C₈carbocyclyl or phenyl ring, wherein the monocyclic ring is optionally substituted with one or more R^b; or

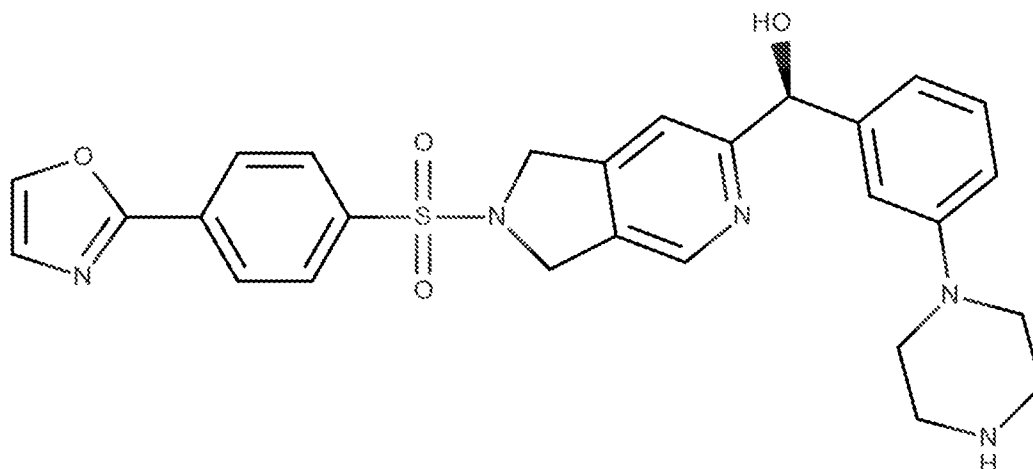
- (ii) a bicyclic 9- to 12-membered ring, comprising a phenyl ring,
 wherein the phenyl ring is fused to an aromatic or partially unsaturated 3- to 8-membered carbocyclic or heterocyclic ring,
 wherein the bicyclic ring contains 0-4 heteroatoms independently selected from the group consisting of O, N, and S, and
 wherein the bicyclic ring is optionally substituted with one or more R^b.

9. The compound of any one of the preceding claims, wherein R^a is .

10. The compound of any one of the preceding claims, wherein each R^b is independently selected

from the group consisting of methyl, , , and .

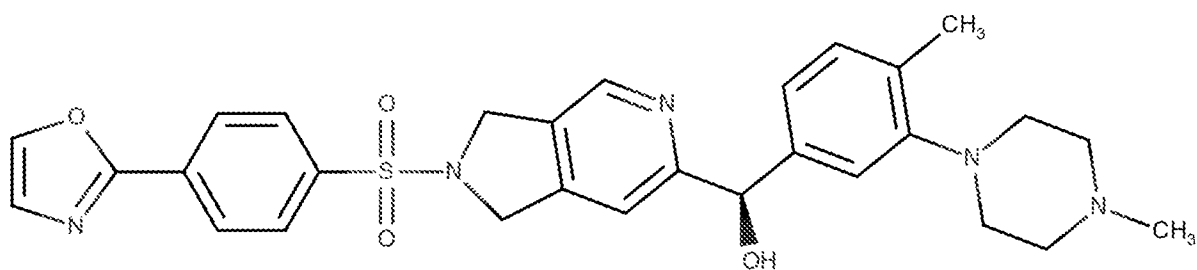
11. The compound of any one of the preceding claims, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

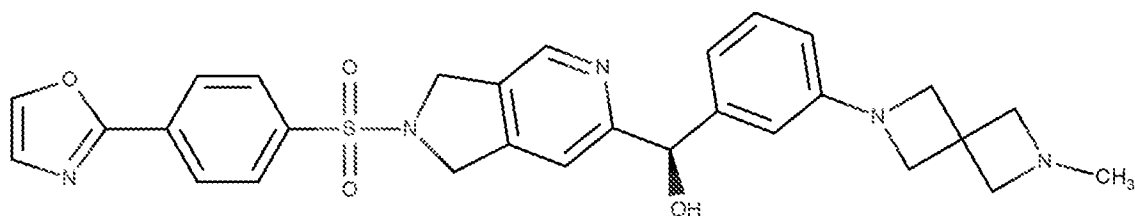
12. The compound of claim 11, wherein the pharmaceutically acceptable salt thereof is a hydrochloride salt.

13. The compound of any one of claims 1-10, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-10, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

15. A pharmaceutical composition, comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/068530

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/18; A61K 31/403; A61K 31/4035; C07D 209/00; C07D 209/44 (2020.01)

CPC - A61K 31/18; A61K 31/403; A61K 31/4035; C07D 209/00; C07D 209/44 (2020.02)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

USPC - 514/415; 514/416; 514/601 (keyword delimited)

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,026,856 A (YATSUNAMI et al) 25 June 1991 (25.06.1991) entire document	1, 2
A	US 2012/0213795 A1 (LI et al) 23 August 2012 (23.08.2012) entire document	1, 2
A	WO 2017/158388 A1 (MISSION THERAPEUTICS LIMITED) 21 September 2017 (21.09.2017) entire document	1, 2
P, A	WO 2019/071073 A1 (FORMA THERAPEUTICS INC) 11 April 2019 (11.04.2019) entire document	1, 2

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

☐ See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

27 March 2020

Date of mailing of the international search report

22 APR 2020

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2019/068530

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 4-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2019/068530

Continued from Box No. III Observations where unity of invention is lacking

Claims 1 and 2 have been analyzed subject to the restriction that the claims read on a compound represented by Formula I: or a pharmaceutically acceptable salt thereof, wherein: X1 is NR; Y1 is CR7; Y2 is CR8; Y3 is CR9; Ring A is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring A is unsubstituted; Ring B is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring B is unsubstituted; R1 and R2 are each selected as -H; R3, R4, R5, and R6 are each -H; R7, R8, and R9 are each -H; each R is H; m is 0; and n is 0.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-3 are drawn to compounds represented by Formula I or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound represented by Formula I: or a pharmaceutically acceptable salt thereof, wherein: X1 is NR; Y1 is CR7; Y2 is CR8; Y3 is CR9; Ring A is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring A is unsubstituted; Ring B is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring B is unsubstituted; R1 and R2 are each selected as -H; R3, R4, R5, and R6 are each -H; R7, R8, and R9 are each -H; each R is H; m is 0; and n is 0. It is believed that claims 1 and 2 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound represented by Formula I: or a pharmaceutically acceptable salt thereof, wherein: X1 is O; Y1 is CR7; Y2 is CR8; Y3 is CR9; Ring A is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring A is unsubstituted; Ring B is a monocyclic 3-membered ring, wherein the ring is saturated, and wherein the ring contains 0 heteroatoms, and wherein Ring B is unsubstituted; R1 and R2 are each selected as -H; R3, R4, R5, and R6 are each -H; R7, R8, and R9 are each -H; each R is H; m is 0; and n is 0. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables X1, Y1, Y2, Y3, Ring A, Ring B, R1, R2, R3, R4, R5, R6, m, n, and accordingly these groups lack unity a priori.

Additionally, even if Groups I+ were considered to share the technical features of a compound of Formula I or a pharmaceutically acceptable salt thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 5,026,856 A to Yatsunami et al.

US 5,026,856 A to Yatsunami et al. teach a compound of Formula I: as shown, wherein: X1 is O; Y1 is CR7; Y2 is CR8; Y3 is CR9; Ring A is a monocyclic 6-membered ring, wherein the ring is aromatic, and wherein Ring A is optionally substituted with one Ra each Ra is selected as C1 aliphatic; Ring B is a bicyclic 9-membered ring, wherein the ring is partially unsaturated, and wherein the ring contains 1 heteroatom selected as N, and wherein Ring B is optionally substituted with one or more Rb; each Rb is selected as oxo; R1 and R2 are each selected as -H; R3, R4, R5, and R6 are each selected as -H; R7, R8, and R9 are each selected as -H; m is 0; and n is 0 (Col. 91, Lns. 34 and 35, ... 2-(p-toluenesulfonyl)-5-phthalimidomethylisoindoline ...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.