METHODS FOR PREPARING TYROSINE RECEPTOR KINASE INHIBITORS

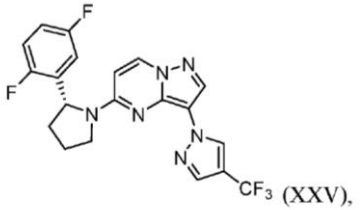
BACKGROUND

[0001] Growth factors are important signaling molecules that promote the growth, development and homeostasis of many cellular systems. Neurotrophins are growth factors that are responsible for central and peripheral neuronal growth, maturation, and death. Neurotrophins activate cell surface receptors called tropomyosin-like receptors, which in turn regulate intracellular kinases called tropomyosin receptor kinases (TRKs). The TRK family of receptors includes TRKA, TRKB, and TRKC, and serve as high affinity cell surface receptors for the growth factors NGF, BDNF, and NT3, respectively. Inhibition of these receptors may lead to the modulation or inhibition of intracellular signaling cascades that regulate cell growth and proliferation, cellular communication between cells that regulate signaling, feedback mechanism, and homeostasis. These growth factors have been implicated in the growth and proliferation of both neuronal and non-neuronal cells.

[0002] TRK inhibitors have the potential to be used in the treatment or prevention of various diseases including inflammatory diseases, infections, autoimmune disorders, stroke, ischemia, cardiac disorder, neurological disorders, fibrogenic disorders, proliferative disorders, hyperproliferative disorders, non-cancer hyper- proliferative disorders, tumors, leukemias, neoplasms, cancers, carcinomas, metabolic diseases, malignant disease, vascular restenosis, psoriasis, atherosclerosis, rheumatoid arthritis, osteoarthritis, chronic pain, neuropathic pain, and other disorders. Despite the widespread therapeutic utility of TRK inhibitors, methods of making these compounds that are amenable to scale-up for large-scale manufacturing processes have remained elusive. Accordingly, there remains a need for compounds useful as intermediates in preparing TRK inhibitors, methods of making these intermediary compounds, and methods of making TRK inhibitors. These needs and others are met by the invention.

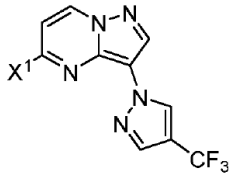
SUMMARY

[0002a] In an aspect, there is provided a method for making a compound having the structure represented by formula (XXV):

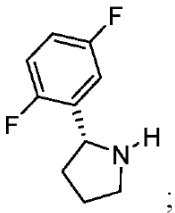


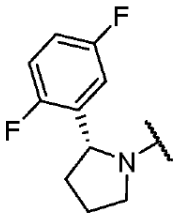
(XXV),

or a pharmaceutically acceptable salt thereof, the method comprising coupling a compound having the structure represented by formula (XXVI):


(XXVI),

and a compound having the structure represented by formula:

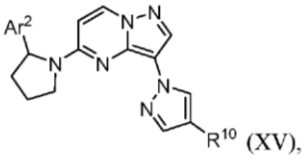

; and


whereby replaces X^1,

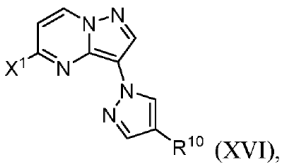
wherein X^1 is a leaving group.

[0002b] In another aspect, there is provided a compound prepared by the method defined above.

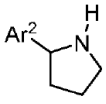
[0002c] In another aspect, there is provided a method for making a compound having the structure represented by formula (XV):

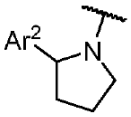

(XV),

or a pharmaceutically acceptable salt thereof, the method comprising coupling a compound of formula (XVI):


(XVI),

and a compound of formula (XVII):

 (XVII),

whereby  replaces X^1;

wherein X^1 is a leaving group;

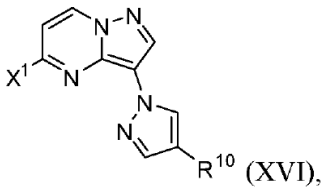
wherein R^{10} is selected from hydrogen, halogen, –CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $–OR^{20}$, $–C(O)R^{20}$, $–S(O)R^{20}$, $–S(O)_2R^{20}$, –(C1-C6 alkyl)OR^{20}, –(C1-C6 alkyl)SR^{20}, –(C1-C6 alkyl)$C(O)R^{20}$, –(C1-C6 alkyl)$S(O)R^{20}$, –(C1-C6 alkyl)$S(O)_2R^{20}$, $–NR^{21}C(O)R^{20}$, $–NR^{21}S(O)_2R^{20}$, $–NR^{22a}R^{22b}$, $–P(O)R^{22a}R^{22b}$, –(C1-C6 alkyl)$NR^{22a}R^{22b}$, –(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;

wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl;

wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8- membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1- C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and

wherein Ar^2 is a C6-C10 aryl or a 5- to 6-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, and C1-C6 haloalkoxy.

[0002d] In another aspect, there is provided a compound having the structure represented by formula (XVI):

 (XVI),

wherein X^1 is a leaving group;

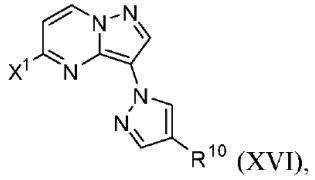
wherein R^{10} is selected from hydrogen, halogen, –CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $–OR^{20,}$ $–C(O)R^{20}$, $–S(O)R^{20}$, $–S(O)_2R^{20}$, –(C1-C6 alkyl)OR^{20}, –(C1-C6 alkyl)SR^{20}, –(C1-C6 alkyl)$C(O)R^{20}$, –(C1-C6 alkyl)$S(O)R^{20}$, –(C1-C6 alkyl)$S(O)_2R^{20}$, $–NR^{21}C(O)R^{20}$, $–NR^{21}S(O)_2R^{20}$, $–NR^{22a}R^{22b}$, $–P(O)R^{22a}R^{22b}$, –(C1-C6 alkyl)$NR^{22a}R^{22b}$, –(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;

wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and

wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8- membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, – NH_2, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1- C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl,

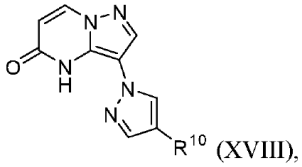
or a pharmaceutically acceptable salt thereof.

[0002e] In another aspect, there is provided a method for making a compound having the structure represented by formula (XVI):



(XVI),

or a salt thereof, the method comprising reacting an amide having the structure represented by formula (XVIII):



(XVIII),

and an activating agent,

wherein X^1 is a leaving group;

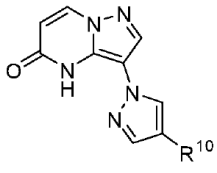
wherein R^{10} is selected from hydrogen, halogen, –CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $–OR^{20}$, $–C(O)R^{20}$, $–S(O)R^{20}$, $–S(O)_2R^{20}$, –(C1-C6 alkyl)OR^{20}, –(C1-C6 alkyl)SR^{20}, –(C1-C6 alkyl)$C(O)R^{20}$, –(C1-C6 alkyl)$S(O)R^{20}$, –(C1-C6 alkyl)$S(O)_2R^{20}$, $–NR^{21}C(O)R^{20}$, $–NR^{21}S(O)_2R^{20}$, $–NR^{22a}R^{22b}$, $–P(O)R^{22a}R^{22b}$, –(C1-C6 alkyl)$NR^{22a}R^{22b}$, –(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;

wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and

wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8- membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, – NH_2, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1- C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl.

[0002f] In another aspect, there is provided a compound prepared by the method defined above.

[0002g] In another aspect, there is provided a compound having the structure represented by formula (XVIII):



(XVIII),

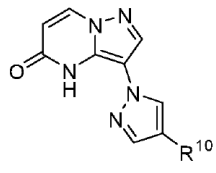
wherein R^{10} is selected from hydrogen, halogen, –CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $–OR^{20}$, $–C(O)R^{20}$, $–S(O)R^{20}$, $–S(O)_2R^{20}$, –(C1-C6 alkyl)OR^{20}, –(C1-C6 alkyl)SR^{20}, –(C1-C6 alkyl)$C(O)R^{20}$, –(C1-C6 alkyl)$S(O)R^{20}$, –(C1-C6 alkyl)$S(O)_2R^{20}$, $–NR^{21}C(O)R^{20}$, $–NR^{21}S(O)_2R^{20}$, $–NR^{22a}R^{22b}$, $–P(O)R^{22a}R^{22b}$, –(C1-C6 alkyl)$NR^{22a}R^{22b}$, –(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;

wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and

wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8- membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $–NH_2$, –OH, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1- C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl,

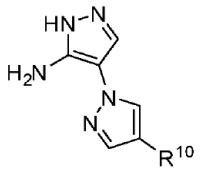
or a salt thereof.

[0002h] In another aspect, there is provided a method for making a compound of formula (XVIII):



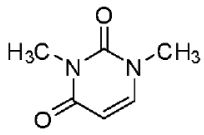
(XVIII),

or a salt thereof, the method comprising reacting an amine having the structure represented by formula (XIX):



(XIX);

and a uracil having the structure represented by formula (XX):



(XX),

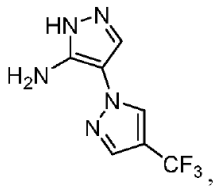
wherein R^{10} is selected from hydrogen, halogen, –CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $–OR^{20}$, $–C(O)R^{20}$, $–S(O)R^{20}$, $–S(O)_2R^{20}$, –(C1-C6 alkyl)OR^{20}, –(C1-C6 alkyl)SR^{20}, –(C1-C6 alkyl)$C(O)R^{20}$, –(C1-C6 alkyl)$S(O)R^{20}$, –(C1-C6 alkyl)$S(O)_2R^{20}$, $–NR^{21}C(O)R^{20}$, $–NR^{21}S(O)_2R^{20}$, $–NR^{22a}R^{22b}$, $–P(O)R^{22a}R^{22b}$, –(C1-C6 alkyl)$NR^{22a}R^{22b}$, –(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;

wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and

wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8- membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, –CN, $– NH_2$, $–OH$, $–NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1- C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl.

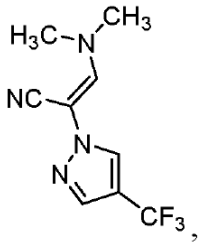
[0002i] In another aspect, there is provided a compound prepared by the method defined above.

[0002j] In another aspect, there is provided a compound having the structure:



or a salt thereof.

[0002k] In another aspect, there is provided a compound having the structure:

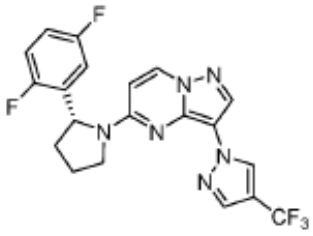


or a salt thereof.

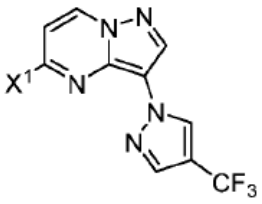
[0003] In accordance with the purpose(s) of the ~~invention~~disclosure, as embodied and broadly described herein, the disclosure~~invention~~, in some ~~embodiments~~examples, relates to pyrazolo[1,5-a]pyrimidine

compounds useful as TRK inhibitors and compounds useful in preparing pyrazolo[1,5-a]pyrimidine compounds, and methods of making and using same.

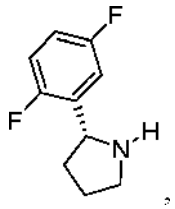
[0004] Thus, in some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure represented by formula (XXV):

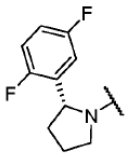

(XXV),

or a pharmaceutically acceptable salt thereof, the method comprising coupling a compound having the structure represented by formula (XXVI):


(XXVI),

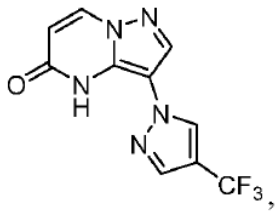
and a compound having the structure represented by formula:



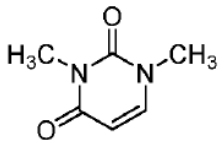
whereby  replaces X^1, and wherein X^1 is a leaving group.

[0005] In some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure:

via reacting the acrylonitrile with a hydrazine; (d) preparing an amide having the structure:

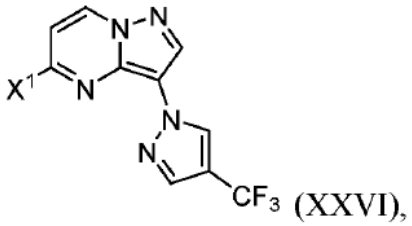


via reacting the amine and a uracil having the structure:



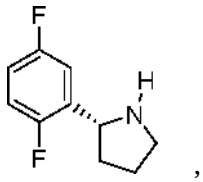
;

(e) preparing a compound having the structure represented by formula (XXVI):



(XXVI),

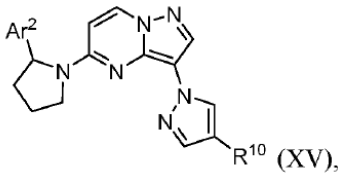
via reacting the amide and a halogenating agent; and (f) preparing the compound of formula (XXV) via coupling the compound of formula (XXVI) and a compound having the structure:



,

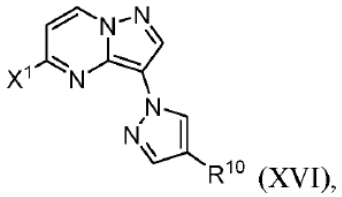
wherein X^1 is a leaving group; and wherein X^2 is a halogen.

[0006] In some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure represented by formula (XV):



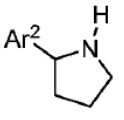
(XV),

or a pharmaceutically acceptable salt thereof, the method comprising coupling a compound of formula (XVI):

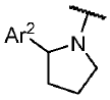


(XVI),

and a compound of formula (XVII):



(XVII),

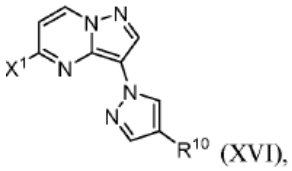
whereby  replaces X^1; wherein X^1 is a leaving group; wherein R^{1° is selected from hydrogen, halogen, -CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $-OR^{20}$, $-C(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, -(C1-C6 alkyl)OR^{20}, -(C1-C6 alkyl)SR^{20}, -(C1-C6 alkyl)$C(O)R^{20}$, -(C1-C6 alkyl)$S(O)R^{20}$, -(C1-C6 alky)$S(O)_2R^{20}$, $-NR^{21}C(O)R^{20}$, $-NR^{21}S(O)_2R^{20}$, $-NR^{22a}R^{22b}$, $-P(O)R^{22a}R^{22b}$, -(C1-C6 alkyl)$NR^{22a}R^{221b}$, -(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^l, wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, $-NH_2$, -OH, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; and wherein Ar^2 is a C6-C10 aryl or a 5- to 6-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, and Cl-C6 haloalkoxy.

[0007] In some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure represented by formula (XV):

when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, -NH_2, -OH, -NO_2, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl; wherein Ar^2 is a C6-C10 aryl or a 5- to 6-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, and Cl-C6 haloalkoxy; and wherein each of R^{31a} and R^{31b} is independently C1-C4 alkyl.

[0008] In some examples~~embodiments~~, the present disclosure provides a compound prepared by a disclosed method.

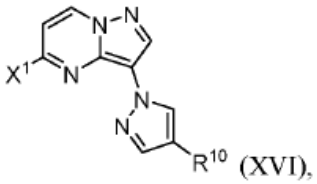
[0009] In some examples~~embodiments~~, the present disclosure provides compounds having the structure represented by formula (XVI):



(XVI),

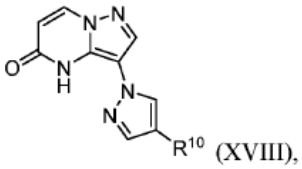
wherein X^1 is a leaving group; wherein R^{10} is selected from hydrogen, halogen, -CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, -OR^{20}, -$C(O)R^{20}$, -$S(O)R^{20}$, -$S(O)2R^{20}$, -(C1-C6 alkyl)OR^{20}, -(C1-C6 alkyl)SR^{20}, -(C1-C6 alkyl)$C(O)R^{20}$, -(C1-C6 alkyl)$S(O)R^{20}$, -(C1-C6 alkyl)$S(O)_2R^{20}$, -$NR^{21}C(O)R^{20}$, -$NR^{21}S(O)_2R^{20}$, -$NR^{22a}R^{22b}$, -$P(O)R^{22a}R^{22b}$, (C1-C6 alkyl)$NR^{22a}R^{22b}$, -(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1;wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, -NH_2, -OH, -NO_2, Cl-C4 alkyl, C2-C4 alkenyl, Cl-C4 haloalkyl, Cl-C4 cyanoalkyl, Cl-C4 hydroxyalkyl, Cl-C4 haloalkoxy, Cl-C4 alkoxy, Cl-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and Cl-C4 aminoalkyl, or a pharmaceutically acceptable salt thereof.

[0010] In some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure represented by formula (XVI):



(XVI),

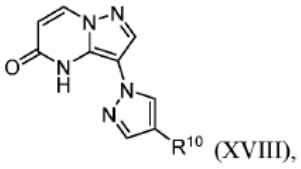
or a pharmaceutically acceptable salt thereof, the method comprising reacting an amide having the structure represented by formula (XVIII):



(XVIII),

and an activating agent, wherein X^1 is a leaving group; wherein R^{10} is selected from hydrogen, halogen, -CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $-OR^{20}$, $-C(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, -(C1-C6 alkyl)OR^{20}, -(C1-C6 alkyl)SR^{20}, -(C1-C6 alkyl)$C(O)R^{20}$, -(C1-C6 alkyl)$S(O)R^{20}$, -(C1-C6 alkyl)$S(O)_2R^{20}$, $-NR^{21}C(O)R^{20}$, $-NR^{21}S(O)_2R^{20}$, $-NR^{22a}R^{22b}$, $-P(O)R^{22a}R^{22b}$, (C1-C6 alkyl)$NR^{22a}R^{22b}$, -(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^l, wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, $-NH_2$, -OH, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl.

[0011] In some examples~~embodiments~~, the present disclosure provides compounds having the structure represented by formula (XVIII):

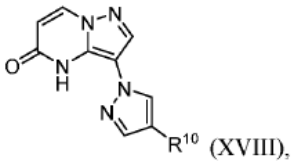


(XVIII),

wherein R^{10} is selected from hydrogen, halogen, -CN, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 cyanoalkyl, $-OR^{20}$, $-C(O)R^{20}$, $-S(O)R^{20}$, $-S(O)_2R^{20}$, -(C1-C6 alkyl)OR^{20}, -(C1-C6

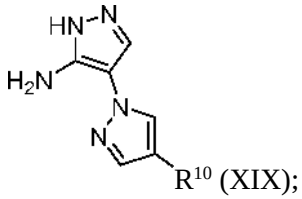
alkyl)SR^{20}, -(C 1-C6 alkyl)$C(O)R^{20}$, -(C1-C6 alkyl)$S(O)R^{20}$, -(C1-C6 alkyl)$S(O)_2R^{20}$, -$NR^{21}C(O)R^{20}$, -$NR^{21}S(O)_2R^{20}$, -$NR^{22a}R^{22b}$, -$P(O)R^{22a}R^{22b}$, (C1-C6 alkyl)$NR^{22a}R^{22b}$, -(C1-C6 alkyl)$P(O)R^{22a}R^{22b}$, and Cy^1; wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and wherein Cy^l, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, $-NH_2$, -OH, $-NO_2$, Cl-C4 alkyl, C2-C4 alkenyl, Cl-C4 haloalkyl, Cl-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, Cl-C4 alkoxy, Cl-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl, or a pharmaceutically acceptable salt thereof.

[0012] In some examples~~embodiments~~, the present disclosure provides methods for making a compound having the structure represented by formula (XVIII):



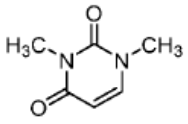
(XVIII),

or a pharmaceutically acceptable salt thereof, the method comprising reacting an amine having the structure represented by formula (XIX):



(XIX);

and a uracil having the structure represented by formula (XX):

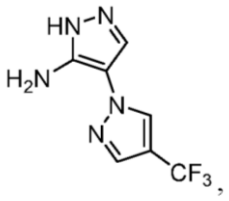


(XX),

wherein R^{10} is selected from hydrogen, halogen, -CN, Cl-C6 alkyl, Cl-C6 haloalkyl, Cl-C6 cyanoalkyl, -OR^{20}, -$C(O)R^{20}$, -$S(O)R^{20}$, -$S(O)_2R^{20}$, -(C1-C6 alkyl)OR^{20}, -(C1-C6 alkyl)SR^{20}, -(C1-C6 alkyl)$C(O)R^{20}$, -(C1-C6 alkyl)$S(O)R^{20}$, -(C1-C6 alkyl)$S(O)_2R^{20}$, -$NR^{21}C(O)R^{20}$, -$NR^{21}S(O)_2R^{20}$, -$NR^{22a}R^{22b}$, -$P(O)R^{22a}R^{22b}$, (C1-C6 alkyl)$NR^{22a}R^{22b}$, -(C1-

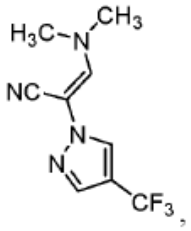
C6 alkyl)P(O)$R^{22a}R^{22b}$, and Cy^1; wherein each of R^{20}, R^{21}, R^{22a}, and R^{22b}, when present, is independently selected from hydrogen, C1-C4 alkyl, and C1-C4 haloalkyl; and wherein Cy^1, when present, is selected from a C3-C8 cycloalkyl, a 3- to 8-membered heterocycloalkyl, a C6-C10 aryl, and a 5- to 10-membered heteroaryl, and is substituted with 0, 1, 2, or 3 groups independently selected from halogen, -CN, $-NH_2$, -OH, $-NO_2$, C1-C4 alkyl, C2-C4 alkenyl, C1-C4 haloalkyl, C1-C4 cyanoalkyl, C1-C4 hydroxyalkyl, C1-C4 haloalkoxy, C1-C4 alkoxy, C1-C4 alkylamino, (C1-C4)(C1-C4) dialkylamino, and C1-C4 aminoalkyl.

[0013] In some examples~~embodiments~~, the present disclosure provides compounds having the structure:



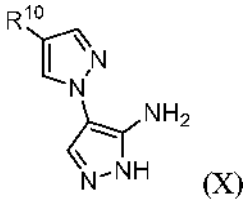
or a pharmaceutically acceptable salt thereof.

[0014] In some examples~~embodiments~~, the present disclosure provides compounds having the structure:



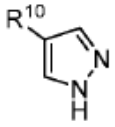
or a pharmaceutically acceptable salt thereof

[0015] In some examples~~embodiments~~, the present disclosure provides a method of preparing a compound of Formula (X):

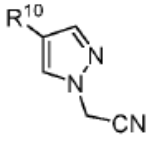


(X)

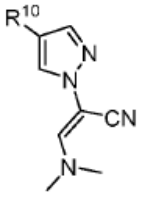
or a salt thereof, comprising one or more of steps (i-1) to (i-3): (i-1) contacting a compound of Formula (VII):


(VII)

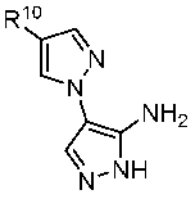
with an acetonitrile addition agent, thereby forming a compound of Formula (VIII):


(VIII);

(i-2) contacting the compound of Formula (VIII) with N,N-dimethylformamide diethyl acetal or a synthetic equivalent thereof, thereby forming a compound of Formula (IX):


(IX); or

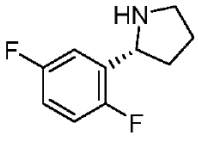
(i-3) contacting the compound of Formula (IX) with hydrazine, thereby forming a compound of Formula (X):


(X)

or a salt thereof, wherein R^{10} is as described above.

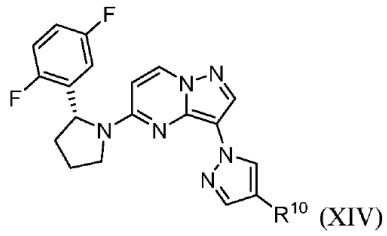
[0016] In some examples~~embodiments~~, the present disclosure provides a use of compound of Formula (VII) in the manufacture of a compound of Formula (X) or a salt thereof, comprising one or more of steps (i-1) to (i-3).

[0017] In some examples~~embodiments~~, the present disclosure provides a method of preparing a compound of Formula (XIV):



(Compound No. 6)

or a salt thereof, thereby forming a compound of Formula (XIV):



(XIV)

or a salt thereof, wherein IV° is as described above.

[0018] In some examples~~embodiments~~, the present disclosure provides a use of a compound of Formula (X) or a salt thereof, in the manufacture of a compound of Formula (XIV) or a salt thereof, comprising one or more of steps (f-1) to (f-3).

[0019] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (VII) and an acetonitrile addition agent. In these types of reactions, a suitable acetonitrile addition agent is a haloacetonitrile such as bromoacetonitrile.

[0020] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (VII) and an acetonitrile addition agent for preparing a compound of Formula (X) or a salt thereof.

[0021] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (VIII) and *N*,*N*-dimethylformamide diethyl acetal or a synthetic equivalent thereof. The term "formamidine acetal" is used in this context to refer to *N*,*N*-dimethylformamide diethyl acetal or a synthetic equivalent thereof.

[0022] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (VIII) and *N*,*N*-dimethylformamide diethyl acetal or a synthetic equivalent thereof, for preparing a compound of Formula (X) or a salt thereof.

[0023] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (IX) and hydrazine.

[0024] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (IX) and hydrazine, useful for preparing a compound of Formula (X) or a salt thereof.

[0025] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (X) or a salt thereof, and Compound No. 11, or a synthetic equivalent thereof.

[0026] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (X) or a salt thereof, and Compound No. 11, or a synthetic equivalent thereof, useful for preparing a compound of Formula (XIV) or a salt thereof.

[0027] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (XII) and a chlorination agent.

[0028] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (XII) and a chlorination agent, useful for preparing a compound of Formula (XIV) or a salt thereof.

[0029] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (XIII) and Compound No. 6 or a salt thereof.

[0030] In some examples~~embodiments~~, the present disclosure provides a combination comprising a compound of Formula (XIII) and Compound No. 6 or a salt thereof, useful for preparing a compound of Formula (XIV) or a salt thereof.

[0031] In some examples~~embodiments~~, the present disclosure provides a compound of any of Formulae (VII)-(X) and (XII)-(XIV), wherein: R^{10} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 3- to 8-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 3- to 8-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1S}; and each R^{1S} independently is halogen, -O-(C_1-C_6 alkyl), or -N(R^{1Sa})$_2$.

[0032] In some examples~~embodiments~~, the present disclosure provides a compound of any of Formulae (X) and (XIV) or a salt thereof, wherein: R^{10} is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 3- to 8-membered heterocycloalkyl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 3- to 8-membered heterocycloalkyl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1S}; and each R^{1S} independently is halogen, -O-(C_1-C_6 alkyl), or -N(R^{1Sa})$_2$.

[0033] In some examples~~embodiments~~, the present disclosure provides a compound being prepared by a method described herein.

[0034] In some examples~~embodiments~~, the present disclosure provides a pharmaceutical composition comprising a compound described herein, and one or more pharmaceutically acceptable carriers or excipients.

[0035] In some examples~~embodiments~~, the present disclosure provides a pharmaceutical composition comprising a compound prepared by a method described herein, and one or more pharmaceutically acceptable carriers or excipients.

[0036] In some examples~~embodiments~~, the present disclosure provides a method of inhibiting a tyrosine receptor kinase (TRK) in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound described herein.

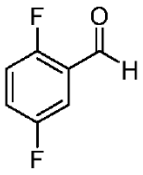
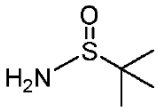
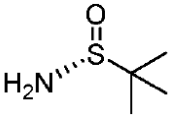
[0037] In some examples~~embodiments~~, the present disclosure provides a use of a compound described herein in the manufacture of a medicament for inhibiting a tyrosine receptor kinase (TRK) in a subject.

[0038] In some examples~~embodiments~~, the present disclosure provides a method of preventing or treating a disease or disorder in a subject, comprising administering to the subject a pharmaceutically effective amount of a compound described herein.

[0039] In some examples~~embodiments~~, the present disclosure provides a use of a compound described herein in the manufacture of a medicament for preventing or treating a disease or disorder in a subject.

[0040] The structures of Formulae (VII)-(X) and (XII)-(XIV) and the structures of Compound Nos. 1-14 are as described in Table 1 below, wherein all variables are as described elsewhere herein.

TABLE 1.

Formula No.	**Structure**	**Compound No.**	**Structure**
		1	
		2	
		2R	
		2S	