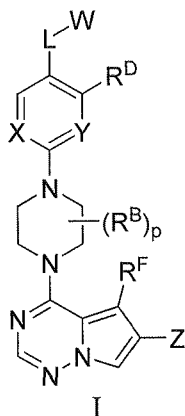
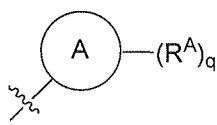


Summary of the Invention

The present disclosure features compounds and compositions for treating or preventing conditions such as mastocytosis and mast cell diseases by modulating the activity of KIT. Such compounds have the structural Formula I:



or a pharmaceutically acceptable salt thereof, wherein:



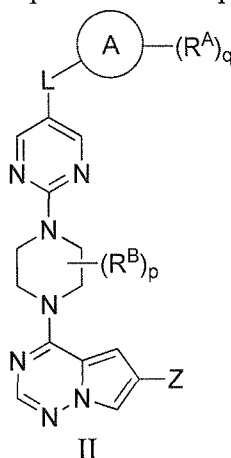
W is selected from hydrogen or wherein Ring A is selected from

monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl or heterocyclyl;
each X and Y is independently selected from CR¹ or N;

Z is C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, monocyclic or bicyclic heterocyclylalkyl; wherein each of C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, monocyclic and bicyclic heterocyclylalkyl is independently substituted with 0-5 occurrences of R^C;

L is selected from a bond, -(C(R²)(R²))_m-, -(C₂-C₆ alkynylene)-, -(C₂-C₆ alkenylene)-, -(C₁-C₆ haloalkylene)-, -(C₁-C₆ heteroalkylene)-, -(C₁-C₆ hydroxyalkylene)-, -C(O)-, -O-, -S-, -S(O)-, -SO₂-, -N(R²)-, -O-(C₁-C₆ alkylene)-, -(C₁-C₆ alkylene)-O-, -N(R²)-CO-, -CO-N(R²)-, -(C₁-C₆ alkylene)-N(R²)-, -N(R²)-(C₁-C₆ alkylene)-, -N(R²)-CO-(C₁-C₆ alkylene)-, -CO-N(R²)-(C₁-C₆ alkylene)-, -N(R²)-SO₂-, -SO₂-N(R²)-, -N(R²)-SO₂-(C₁-C₆ alkylene)-, or -SO₂-N(R²)-(C₁-C₆ alkylene)-;

In one aspect, the present disclosure provides a compound of Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

Z is selected from C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, and monocyclic or bicyclic heterocyclylalkyl; wherein each of C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, monocyclic and bicyclic heterocyclylalkyl is independently substituted with 0-5 occurrences of R^C;

L is selected from a bond, -(C(R²)(R²))_m-, -(C₂-C₆ alkynylene)-, -(C₂-C₆ alkenylene)-, -(C₁-C₆ haloalkylene)-, -(C₁-C₆ heteroalkylene)-, -(C₁-C₆ hydroxyalkylene)-, -C(O)-, -O-, -S-, -S(O), -S(O)₂-, -N(R²)-, -O-(C₁-C₆ alkylene)-, -(C₁-C₆ alkylene)-O-, -N(R²)-C(O)-, -C(O)-N(R²)-, -(C₁-C₆ alkylene)-N(R²)-, -N(R²)-(C₁-C₆ alkylene)-, -N(R²)-C(O)-(C₁-C₆ alkylene)-, -C(O)-N(R²)-(C₁-C₆ alkylene)-, -N(R²)-S(O)₂-, -S(O)₂-N(R²)-, -N(R²)-S(O)₂-(C₁-C₆ alkylene)-, and -S(O)₂-N(R²)-(C₁-C₆ alkylene)-;

each R^A and R^B is independently selected from C₁-C₆ alkyl, C₁-C₆ cycloalkyl, C₁-C₆ heterocyclyl, halo, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, monocyclic or bicyclic aralkyl, -N(R²)(R²), cyano, and -OR²;

each R^C is independently selected from C₁-C₆ alkyl, C₁-C₆ alkynyl, halo, C₁-C₆ heteroalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aryloxy, monocyclic or bicyclic aralkyl, monocyclic or

bicyclic heterocyclyl, monocyclic or bicyclic heterocyclalkyl, nitro, cyano, $-C(O)R^2$, $-OC(O)R^2$, $-C(O)OR^2$, $-SR^2$, $-S(O)_2R^2$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^2$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^2$, $-NR^2S(O)_2R^2$, $-P(O)(R^2)(R^2)$, and $-OR^2$; wherein each of heteroalkyl, haloalkyl, haloalkoxy, alkyl, alkynyl, cycloalkyl, aryl, aryloxy, aralkyl, heterocyclyl, heterocyclalkyl is independently substituted with 0-5 occurrences of R^a ; or 2 R^C together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocycl ring substituted with 0-5 occurrences of R^a ;

each R^2 is independently selected from hydrogen, hydroxyl, halo, thiol, C_1-C_6 thioalkyl, $-NR''R''$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclalkyl, wherein each of C_1-C_6 alkyl, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R^b , or 2 R^2 together with the atoms to which they are attached form a cycloalkyl or heterocycl ring;

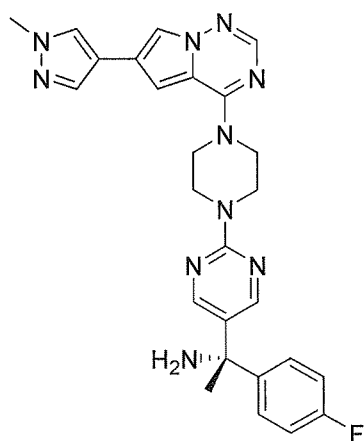
each R^a and R^b is independently selected from hydrogen, halo, cyano, hydroxyl, C_1-C_6 alkoxy, $-C(O)R'$, $C(O)OR'$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, $-NR'R'$, and cycloalkyl, wherein cycloalkyl is substituted with 0-5 occurrences of R' ;

each R' is hydrogen, hydroxyl, or C_1-C_6 alkyl;

each R'' is hydrogen, C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-NR'R'$; or $-C(S)-NR'R'$; and

m, p, and q are each independently 0, 1, 2, 3, or 4.

In another aspect, the present disclosure provides a compound which is:



or a pharmaceutically acceptable salt thereof.

In yet another aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as disclosed herein.

Any of the compounds disclosed herein may be used to treat any of the diseases disclosed herein.

5 In an aspect, there is provided the use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating mastocytosis.

In another aspect, there is provided the use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating
10 gastrointestinal stromal tumor.

In a further aspect, there is provided the use of a compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating acute myeloid leukemia.

The present disclosure also relates to the use of a compound as disclosed herein or a
15 pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by mutant KIT, wherein said KIT has a mutation in Exon 9.

The present disclosure also relates to the use of a compound as disclosed herein or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by mutant KIT, wherein said KIT has a mutation in Exon 11.

20 The present disclosure further relates to the use of a compound as disclosed herein or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by mutant KIT, wherein said KIT has a mutation in Exon 17.

The present disclosure further relates to the use of a compound as disclosed herein or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating
25 a condition mediated by mutant KIT, wherein said KIT is mutated at residue 816.

The present disclosure also relates to the use of a compound as disclosed herein or a pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by mutant PDGFR α , wherein said PDGFR α has a mutation in Exon 18.

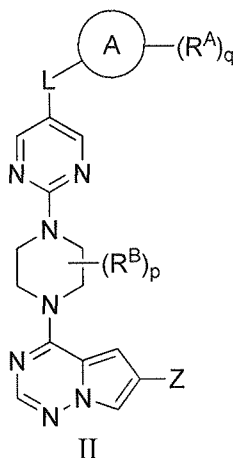
The present disclosure also relates to the use of a compound as disclosed herein or a
30 pharmaceutical composition as disclosed above in the manufacture of a medicament for treating a condition mediated by KIT.

The present disclosure further relates to the use of a compound as disclosed herein or a pharmaceutical composition as disclosed above, in combination with a second agent, wherein the second agent is active against a mutant KIT having a mutation in Exon 9 or Exon 11, in the manufacture of a medicament for treating a condition mediated by KIT.

The present disclosure further relates to the use of (a) a compound as disclosed herein or a pharmaceutical composition as disclosed above; (b) an agent active against mutant KIT A, wherein such mutant KIT A has a mutation in Exon 9 or Exon 11; and (c) an agent active against a mutant KIT B, wherein such mutant KIT B has a mutation that is not in Exon 9 or 11, in the manufacture of a medicament for treating a condition mediated by KIT.

We claim:

1. A compound of Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from monocyclic or bicyclic aryl, monocyclic or bicyclic heteroaryl, cycloalkyl and heterocyclyl;

Z is selected from C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, and monocyclic or bicyclic heterocyclylalkyl; wherein each of C₁-C₆ alkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aralkyl, monocyclic or bicyclic heteroaryl, monocyclic or bicyclic heterocyclyl, monocyclic and bicyclic heterocyclylalkyl is independently substituted with 0-5 occurrences of R^C;

L is selected from a bond, -(C(R²)(R²))_m-, -(C₂-C₆ alkynylene)-, -(C₂-C₆ alkenylene)-, -(C₁-C₆ haloalkylene)-, -(C₁-C₆ heteroalkylene)-, -(C₁-C₆ hydroxyalkylene)-, -C(O)-, -O-, -S-, -S(O), -S(O)₂-, -N(R²)-, -O-(C₁-C₆ alkylene)-, -(C₁-C₆ alkylene)-O-, -N(R²)-C(O)-, -C(O)-N(R²)-, -(C₁-C₆ alkylene)-N(R²)-, -N(R²)-(C₁-C₆ alkylene)-, -N(R²)-C(O)-(C₁-C₆ alkylene)-, -C(O)-N(R²)-(C₁-C₆ alkylene)-, -N(R²)-S(O)₂-, -S(O)₂-N(R²)-, -N(R²)-S(O)₂-(C₁-C₆ alkylene)-, and -S(O)₂-N(R²)-(C₁-C₆ alkylene)-;

each R^A and R^B is independently selected from C₁-C₆ alkyl, C₁-C₆ cycloalkyl, C₁-C₆ heterocyclyl, halo, C₁-C₆ haloalkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ heteroalkyl, monocyclic or bicyclic aralkyl, -N(R²)(R²), cyano, and -OR²;

each R^C is independently selected from C₁-C₆ alkyl, C₁-C₆ alkynyl, halo, C₁-C₆ heteroalkyl, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, cycloalkyl, monocyclic or bicyclic aryl, monocyclic or bicyclic aryloxy, monocyclic or bicyclic aralkyl, monocyclic or

bicyclic heterocyclyl, monocyclic or bicyclic heterocyclalkyl, nitro, cyano, $-C(O)R^2$, $-OC(O)R^2$, $-C(O)OR^2$, $-SR^2$, $-S(O)_2R^2$, $-S(O)_2-N(R^2)(R^2)$, $-(C_1-C_6 \text{ alkylene})-S(O)_2-N(R^2)(R^2)$, $-N(R^2)(R^2)$, $-C(O)-N(R^2)(R^2)$, $-N(R^2)(R^2)-C(O)R^2$, $-(C_1-C_6 \text{ alkylene})-N(R^2)-C(O)R^2$, $-NR^2S(O)_2R^2$, $-P(O)(R^2)(R^2)$, and $-OR^2$; wherein each of heteroalkyl, haloalkyl, haloalkoxy, alkyl, alkynyl, cycloalkyl, aryl, aryloxy, aralkyl, heterocyclyl, heterocyclalkyl is independently substituted with 0-5 occurrences of R^a ; or 2 R^C together with the carbon atom(s) to which they are attached form a cycloalkyl or heterocycl ring substituted with 0-5 occurrences of R^a ;

each R^2 is independently selected from hydrogen, hydroxyl, halo, thiol, C_1-C_6 thioalkyl, $-NR''R''$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclalkyl, wherein each of C_1-C_6 alkyl, cycloalkyl and heterocyclyl is independently substituted with 0-5 occurrences of R^b , or 2 R^2 together with the atoms to which they are attached form a cycloalkyl or heterocycl ring;

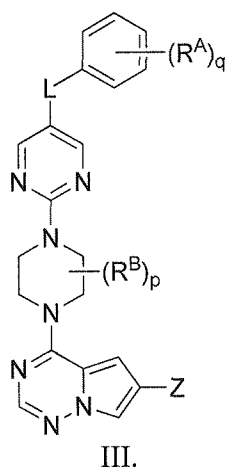
each R^a and R^b is independently selected from hydrogen, halo, cyano, hydroxyl, C_1-C_6 alkoxy, $-C(O)R'$, $C(O)OR'$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_1-C_6 hydroxyalkyl, $-NR'R'$, and cycloalkyl, wherein cycloalkyl is substituted with 0-5 occurrences of R' ;

each R' is hydrogen, hydroxyl, or C_1-C_6 alkyl;

each R'' is hydrogen, C_1-C_6 alkyl, $-C(O)-C_1-C_6$ alkyl, $-C(O)-NR'R'$; or $-C(S)-NR'R'$; and

m , p , and q are each independently 0, 1, 2, 3, or 4.

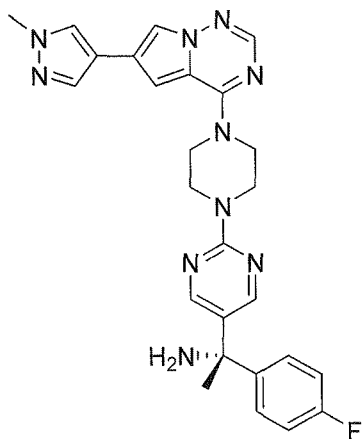
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula III:



3. The compound of claim 1 or claim 2, wherein L is $-(C(R^2)(R^2))_m-$.

4. The compound of claim 1 or claim 3, wherein A is monocyclic or bicyclic aryl.
5. The compound of any one of claims 1 to 4, wherein Z is monocyclic or bicyclic aryl, optionally wherein Z is phenyl.
6. The compound of any one of claims 1 to 4, wherein Z is monocyclic or bicyclic heteroaryl.
7. The compound of any one of claims 1 to 4, wherein Z is monocyclic heteroaryl, optionally wherein Z is selected from pyrazolyl, isoxazolyl, thiophenyl, thiazolyl, and pyridyl.
8. The compound of any one of claims 1 to 4, wherein Z is monocyclic or bicyclic heterocyclyl.
9. The compound of any one of claims 1 to 8, wherein R^A is fluoro and q is 1.

10. A compound which is:



or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of claims 1 to 10 or a pharmaceutically acceptable salt thereof.

12. Use of a compound of any of claims 1 to 10 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating mastocytosis.
13. Use of a compound of any of claims 1 to 10 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating gastrointestinal stromal tumor.
14. Use of a compound of any of claims 1 to 10 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating acute myeloid leukemia.
15. The use according to claim 12, wherein the mastocytosis is selected from cutaneous mastocytosis (CM) and systemic mastocytosis (SM).
16. The use according to claim 15, wherein the systemic mastocytosis is selected from indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM), aggressive systemic mastocytosis (ASM), SM associated hematologic non-mast cell lineage disease (SM-AHNMD), and mast cell leukemia (MCL).