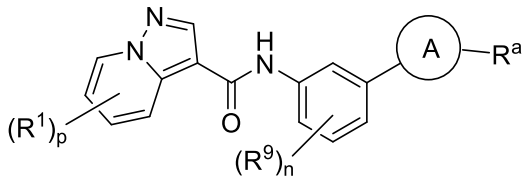
chronic urticaria, and all currently recommended treatment options are intended only to control and prevent the symptoms of chronic urticaria.

[0005] Wild-type c-kit plays a central role in mast cell survival, proliferation, and activation. Recently in clinical trials, c-kit inhibition has shown positive responses in mast cell mediated diseases. For example, c-kit inhibition in chronic inducible urticaria and chronic spontaneous urticaria has been shown to be an effective treatment in a phase I trial (inducible) and phase 1 and 2 (spontaneous) using a monoclonal antibody, and a c-kit small molecule inhibitor has also shown modulation of tryptase, a mast cell mediator, in normal healthy volunteers and in a phase 1 trial of chronic inducible urticaria the inhibitor has been shown to be an effective treatment. There is need for treatments to target mast cells directly through highly selective inhibition of c-kit to achieve broad symptomatic relief across a range of mast cell mediated diseases.

SUMMARY

[0006] Provided herein are compounds, or pharmaceutically acceptable salts thereof, and compositions which are useful for inhibiting wild type c-kit kinase and for treating diseases or disorders mediated by wild type c-kit kinase. The compounds of the disclosure are potent inhibitors of c-kit kinase (see Table 2 in Example 290). Some compounds of the disclosure are orally bioavailable, selective over other kinases such FLT3 kinase and PDGFR and have minimal CNS penetration to reduce CNS side effects.

[0007] One example of the disclosure is a compound represented by Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

[0008] Ring A is selected from tetrazole or triazole, wherein said tetrazole or triazole is optionally substituted with R^a;

wherein R^a is selected from hydrogen, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{0-5}alkylphenyl, C_{0-5}alkylC_{3-6}cycloalkyl, C_{0-5}alkylC_{6-10}spirocycloalkyl, C_{0-5}alkylC_{5-10}bridgedbicycloalkyl, and C_{0-5}alkyl(4-6 membered heterocycle), or C_{0-5}alkyl(7-10 membered spiroheterocycle) or C_{0-5}alkyl(5-10 membered bridgedbicycloheterocycle, each

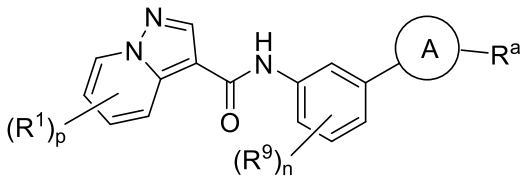
(C_{0-4}alkyl)-(4-6 membered heterocycle containing at least one O or N), wherein said heterocycle is optionally substituted with 1-3 C_{0-3}alkylOH;

each R^9 is independently selected from C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, CN, and C_{3-4}cycloalkyl;

n is 1 or 2; and

p is 0, 1 or 2.

[0008a] In one aspect, the disclosure relates to a compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from tetrazole or triazole, wherein said tetrazole or triazole is optionally substituted with Ra;

wherein R^a is selected from hydrogen, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{0-5}alkylphenyl, C_{0-5}alkylC_{3-6}cycloalkyl, C_{0-5}alkylC_{6-10}spirocycloalkyl, C_{0-5}alkylC_{5-10}bridgedbicycloalkyl, C_{0-5}alkyl(4-6 membered heterocycle), C_{0-5}alkyl(7-10 membered spiroheterocycle) and C_{0-5}alkyl(5-10 membered bridgedbicycloheterocycle), wherein said heterocycle, spiroheterocycle, and bridgedbicycloheterocycle contain at least one N or O, and said alkyl, haloalkyl, phenyl, cycloalkyl, spirocycloalkyl, bridgedbicycloalkyl, heterocycle, spiroheterocycle, or bridgedbicycloheterocycle is optionally substituted with 1-5 R^b, wherein:

each R^b is independently selected from OH, CN, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-5}cycloalkoxy, SO_2C_{1-4}alkyl, SO_2C_{1-4}haloalkyl, C(O)OC_{1-4}alkyl, SO_2(C_{0-2}alkyl)(4-6 membered heterocycle containing at least one O or N), SO_2(C_{1-4}alkyl)C_{1-4}haloalkoxy, SO_2(C_{1-4}alkyl)C_{1-4}alkoxy(C_{0-1}alkoxy), SO_2(C_{1-4}alkyl)OH, SO_2(C_{0-2}alkyl)C_{3-6}cycloalkyl, C_{1-3}alkyl, C_{1-5}haloalkyl, halogen, and C_{1-2}alkylOH, further wherein said cycloalkyl is optionally substituted with C_{1-3}alkyl;

each R^1 is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{0-4}alkylOH, C_{6-10}spirocycloalkyl, C_{0-6}alkylC_{1-6}alkoxy, C_{0-4}alkylC_{1-6}haloalkoxy, NH_2, NHC_{1-6}alkyl, $N(C_{1-6}alkyl)_2$, NH-(4-6 membered heterocycle or 5-6 membered heteroaryl containing at least one O or N), 4-6 membered heterocycle, 7-10 membered fused bicycloheterocycle, 7-10 membered spiroheterocycle, and 5-6 membered heteroaryl containing at least two N, wherein said heterocycle, fused bicycloheterocycle, and spiroheterocycle contain at least one N or O, and said alkyl, haloalkyl, alkoxy, cycloalkyl, spirocycloalkyl, heterocycle, or heteroaryl is optionally substituted with 1-3 R^e;

each R^e is independently selected from deuterium, deuterated C_{1-4}alkyl, deuterated C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, C_{0-3}alkyl-$S(O)_2C_{1-3}$alkyl, C_{0-3}alkyl-$S(O)(NH)C_{1-3}$alkyl, $(C_{1-4}alkyl)P(O)(C_{1-3}alkyl)_2$, C_{1-4}alkyl, CN, CHF_2, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, C_{0-4}alkylOH, $C_{2-5}alkyl(OH)_2$, $C_{1-4}alkyl(OH)(C_1-C_4alkoxy)$, $C_{2-5}alkyl(OH)(C_{1-5}alkoxy)(C_{1-5}alkoxy)$, C_{0-4}alkylC_{1-4}alkoxy, C_{1-3}alkoxyC_{1-3}alkoxy, NH_2, $NH(C_{1-6}alkyl)$, $N(C_{1-6}alkyl)_2$, and $(C_{0-4}alkyl)$-(4-6 membered heterocycle containing at least one O or N), wherein said heterocycle is optionally substituted with 1-3 C_{0-3}alkylOH, or C_{1-3}alkyl;

each R^9 is independently selected from C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, CN, and C_{3-4}cycloalkyl;

n is 1 or 2; and

p is 0, 1 or 2.

[0009] Another example of the disclosure is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound of the disclosure, or a pharmaceutically acceptable salt thereof. In one example, the composition is for treating a disease or disorder mediated by wild type c-kit kinase. In another example, the composition is for inhibiting wild type c-kit kinase.

[0009a] In another aspect, the disclosure relates a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

[0010] Another example of the disclosure is a method of treating a subject suffering from a disease or disorder mediated by wild type c-kit kinase. The method comprises administrating to the subject an effective amount of a compound of the disclosure, or

pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

[0011] Another example of the disclosure is a method of inhibiting wild type c-kit kinase in a subject in need thereof. The method comprises administrating to the subject in need thereof an effective amount of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or an effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound of the disclosure, or a pharmaceutically acceptable salt thereof.

[0012] Another example of the disclosure is the use of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of the disclosure and a pharmaceutically acceptable carrier or excipient in the manufacture of a medicament for the treatment of medical condition mediated by wild type c-kit kinase.

[0013] Another example of the disclosure is the use of a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of the disclosure and a pharmaceutically acceptable carrier or excipient in the manufacture of a medicament for inhibiting wild type c-kit kinase in a subject in need thereof.

[0014] Another example of the disclosure is a compound of the disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutically composition comprising a compound of the disclosure and a pharmaceutically acceptable carrier or excipient for the treatment of a medical condition mediated by wild type c-kit kinase.

[0015] Another example of the disclosure is a compound of the disclosure or a pharmaceutically acceptable salt thereof, or a pharmaceutically composition comprising a compound of the disclosure and a pharmaceutically acceptable carrier or excipient for inhibiting wild type c-kit kinase in a subject in need thereof.

[0015a] In another aspect, the disclosure relates to use of a compound as described herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein in the manufacture of a medicament for the treatment of a subject suffering from a disease or disorder wherein

(i) the disease or disorder is selected from urticaria, dermatosis, idiopathic anaphylaxis, asthma, hereditary alpha tryptasemia (HAT), neurofibromatosis, idiopathic pulmonary fibrosis, bullous pemphigoid, prurigo nodularis, age-related macular degeneration, allergic conjunctivitis, allergic rhinitis, alpha-1 antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis (AML), bronchiectasis, Celiac disease, chronic graft verse host disease, chronic rhinosinusitis with nasal polyps, colorectal cancer, dermatitis herpetiformis, irritable bowel syndrome (IBS), fibromyalgia, fibrosis, food allergies, insulin-dependent diabetes mellitus, mast cell leukemia, migraine, multiple sclerosis, Parkinson's disease, psoriasis, rheumatoid arthritis, pulmonary arterial hypertension (PAH), inflammatory bowel disease (IBD), scleroderma, dermatosis, dermatitis herpetiformis, melanoma, gastrointestinal stromal tumor, mast cell tumor, anaphylactic syndrome, idiopathic anaphylaxis, eosinophilic esophagitis and mastocytosis;

(ii) the disease or disorder is chronic urticaria; or

(iii) the disease or disorder is chronic spontaneous urticaria (CSU),

optionally wherein the subject is resistant to antihistamine treatment (i.e., the subject remains symptomatic despite antihistamine treatment).

[0015b] In another aspect, the disclosure relates to a compound as described herein, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition as described herein, for use in therapy.

DETAILED DESCRIPTION OF THE INVENTION

[0016] An object of this disclosure is to provide novel compounds and compositions with highly selective, potent activity against wild type c-kit kinase for the safe and effective treatment of mast cell associated disease in a subject. For example, the IC_{50} values for inhibition of phospho kit provided in Table 2 of Example 290 demonstrate that these compounds are potent inhibitors of c-kit. The term "KIT" or "kit" refers to a human tyrosine kinase that may be referred to as mast/stem cell growth factor receptor (SCFR), proto-oncogene c-kit, tyrosine-protein kinase kit or CD117.

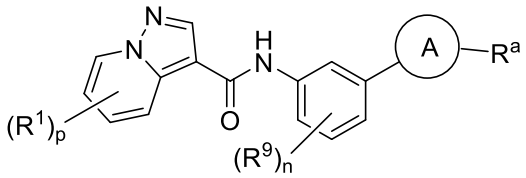
[0017] In treating these mast cell associated diseases, especially chronic disorders such as urticaria and asthma, any new therapy should be well-tolerated. The compounds of the disclosure aim to provide treatments having desirable efficacy, safety, and pharmaceutical properties for the treatment of c-kit mediated diseases. In some aspects, compounds of the disclosure are orally administered. In some aspects, compounds of the disclosure are selective inhibitors of c-kit kinase. Selective inhibitors selectively reduce target signaling activity relative to off-target signaling activity, via direct or indirect interaction with the target, which leads to an increased probability of clinical success in comparison with a non-selective inhibitors. In some aspects, compounds of the disclosure have low CNS penetration, which is a desirable property for reducing and minimizing side effects of chronic treatment. Compounds with low CNS penetration often have high levels or active transport out of the brain, *i.e.*, high efflux ratios from the CNS.

[0018] Compounds of the disclosure are selective c-kit inhibitors. As used herein, a "selective c-kit inhibitor" refers to a compound or a pharmaceutically acceptable salt thereof that has the ability to selectively inhibit c-kit kinase over other targets. More specifically, a selective c-kit inhibitor has the ability to selectively inhibit c-kit over another kinase. In some aspects, compounds of the disclosure are selective for c-kit over FLT3 kinase and PDGFR kinase. A

CLAIMS

What is claimed is:

1. A compound having the structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from tetrazole or triazole, wherein said tetrazole or triazole is optionally substituted with R^a;

wherein R^a is selected from hydrogen, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{0-5}alkylphenyl, C_{0-5}alkylC_{3-6}cycloalkyl, C_{0-5}alkylC_{6-10}spirocycloalkyl, C_{0-5}alkylC_{5-10}bridgedbicycloalkyl, C_{0-5}alkyl(4-6 membered heterocycle), C_{0-5}alkyl(7-10 membered spiroheterocycle) and C_{0-5}alkyl(5-10 membered bridgedbicycloheterocycle), wherein said heterocycle, spiroheterocycle, and bridgedbicycloheterocycle contain at least one N or O, and said alkyl, haloalkyl, phenyl, cycloalkyl, spirocycloalkyl, bridgedbicycloalkyl, heterocycle, spiroheterocycle, or bridgedbicycloheterocycle is optionally substituted with 1-5 R^b, wherein:

each R^b is independently selected from OH, CN, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{3-5}cycloalkoxy, SO_2C_{1-4}alkyl, SO_2C_{1-4}haloalkyl, C(O)OC_{1-4}alkyl, SO_2(C_{0-2}alkyl)(4-6 membered heterocycle containing at least one O or N), SO_2(C_{1-4}alkyl)C_{1-4}haloalkoxy, SO_2(C_{1-4}alkyl)C_{1-4}alkoxy(C_{0-1}alkoxy), SO_2(C_{1-4}alkyl)OH, SO_2(C_{0-2}alkyl)C_{3-6}cycloalkyl, C_{1-3}alkyl, C_{1-5}haloalkyl, halogen, and C_{1-2}alkylOH, further wherein said cycloalkyl is optionally substituted with C_{1-3}alkyl;

each R^1 is independently selected from halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{3-6}cycloalkyl, C_{0-4}alkylOH, C_{6-10}spirocycloalkyl, C_{0-6}alkylC_{1-6}alkoxy, C_{0-4}alkylC_{1-6}haloalkoxy, NH_2, NHC_{1-6}alkyl, N(C_{1-6}alkyl)$_2$, NH-(4-6 membered heterocycle or 5-6 membered heteroaryl containing at least one O or N), 4-6 membered heterocycle, 7-10 membered fused bicycloheterocycle, 7-10 membered spiroheterocycle, and 5-6 membered heteroaryl containing at least two N, wherein said heterocycle,

fused bicycloheterocycle, and spiroheterocycle contain at least one N or O, and said alkyl, haloalkyl, alkoxy, cycloalkyl, spirocycloalkyl, heterocycle, or heteroaryl is optionally substituted with 1-3 R^e;

each R^e is independently selected from deuterium, deuterated C_{1-4}alkyl, deuterated C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, C_{0-3}alkyl-$S(O)_2C_{1-3}$alkyl, C_{0-3}alkyl-S(O)(NH)C_{1-3}alkyl, (C_{1-4}alkyl)P(O)(C_{1-3}alkyl), C_{1-4}alkyl, CN, CHF_2, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, C_{0-4}alkylOH, C_{2-5}alkyl$(OH)_2$, C_{1-4}alkyl(OH)(C_1-C_4alkoxy), C_{2-5}alkyl(OH)(C_{1-5}alkoxy)(C_{1-5}alkoxy), C_{0-4}alkylC_{1-4}alkoxy, C_{1-3}alkyoxyC_{1-3}alkoxy, NH_2, NH(C_{1-6}alkyl), N(C_{1-6}alkyl)$_2$, and (C_{0-4}alkyl)-(4-6 membered heterocycle containing at least one O or N), wherein said heterocycle is optionally substituted with 1-3 C_{0-3}alkylOH, or C_{1-3}alkyl;

each R^9 is independently selected from C_{1-3}alkyl, C_{1-3}haloalkyl, halogen, CN, and C_{3-4}cycloalkyl;

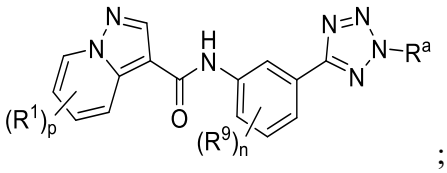
n is 1 or 2; and

p is 0, 1 or 2;

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein

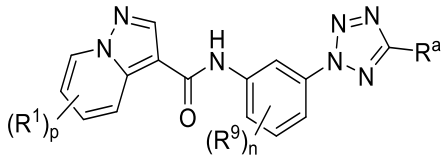
each R^e is independently selected from deuterium, deuterated C_{1-4}alkyl, deuterated C_{1-4}alkoxy, C_{1-4}haloalkoxy, halogen, C_{0-3}alkyl-$S(O)_2C_{1-3}$alkyl, C_{0-3}alkyl-S(O)(NH)C_{1-3}alkyl, (C_{1-4}alkyl)P(O)(C_{1-3}alkyl), C_{1-4}alkyl, CN, CHF_2, C_{3-6}cycloalkyl, C_{1-4}haloalkyl, C_{0-4}alkylOH, C_{1-4}alkyl(OH)(C_1-C_4alkoxy), C_{0-4}alkylC_{1-4}alkoxy, C_{1-3}alkyoxyC_{1-3}alkoxy, NH_2, NH(C_{1-6}alkyl), N(C_{1-6}alkyl)$_2$, and (C_{0-4}alkyl)-(4-6 membered heterocycle containing at least one O or N), wherein said heterocycle is optionally substituted with 1-3 C_{0-3}alkylOH.

3. The compound of claim 1 or 2 having the structure of Formula (IIa), (IIb), (IIIa) or (IIIb):

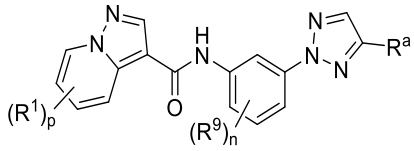


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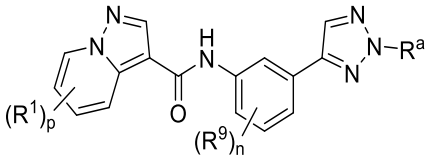
(IIa)


;

(IIb)


; or

(IIIa)


,

(IIIb)

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein p is 0.

5. The compound of any one of claims 1-3 or a pharmaceutically acceptable salt thereof, wherein p is 1 or 2.

6. The compound of any one of claims 1-5 or pharmaceutically acceptable salt thereof, wherein:

R^a is selected from hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{0-3}alkylphenyl, C_{0-4}alkylC_{3-6}cycloalkyl, C_{0-3}alkylC_{6-10}spirocycloalkyl, C_{0-3}alkyl(C_{5-8} bridgedbicycloalkyl), C_{0-5}alkyl(4-6 membered heterocycle containing at least one N or O), C_{0-3}alkyl(7-10 membered spiroheterocycle containing at least one N or O), and C_{0-3}alkyl(5-10 membered bridged bicycloheterocycle containing at least one O or N), wherein:

i) said alkyl or haloalkyl is optionally substituted with 1-5 R^b each independently selected from C_{1-5}alkoxy, C_{1-5}haloalkoxy, OH and CN;

ii) said cycloalkyl, spirocycloalkyl, or phenyl is optionally substituted with 1-2 R^b each independently selected from methyl, halogen, C_{1-3}haloalkyl, C_{1-3}alkoxy, and C_{0-3}alkylOH; and

iii) said heterocycle is optionally substituted with one R^b selected from SO_2C_{1-5}alkyl, SO_2C_{1-5}haloalkyl, $C(O)OC_{1-4}$alkyl, SO_2(4-6 membered heterocycle containing at least one O or N), $SO_2(C_{1-3}alkyl)C_{1-3}$haloalkoxy, $SO_2(C_{1-3}alkyl)C_{1-3}$alkoxy, $SO_2(C_{1-4}alkyl)OH$, $SO_2(C_{1-3}alkyl)C_{1-3}$alkoxy(methoxy), $SO_2(C_{0-2}alkyl)C_{3-6}$cycloalkyl and C_{1-4} haloalkyl, further wherein said cycloalkyl is optionally substituted with C_{1-2}alkyl.

7. The compound of any one of claims 1-3, 5 and 6 or pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from halogen, C_{1-4}alkyl, C_{1-4}haloalkyl, C_{0-4}alkylOH, $C_{0-4}alkylC_{1-6}$alkoxy, $C_{0-4}alkylC_{1-6}$haloalkoxy, C_{3-4}cycloalkyl, NH_2, NHC_{1-5}alkyl, $N(C_{1-3}alkyl)_2$, NH-(4-6 membered heterocycle containing at least one O), NH-(5-6 membered heteroaryl containing at least one N), 4-6 membered heterocycle, 7-9 membered fused bicycloheterocycle, 7-10 membered spiroheterocycle, and 5-6 membered heteroaryl containing at least two N, wherein said heterocycle, fused bicycloheterocycle, and spiroheterocycle contain at least one N or O, and wherein:

i) said alkyl, haloalkyl, or alkoxy is optionally substituted with 1-3 R^e each independently selected from deuterium, deuterated C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-4}haloalkoxy, C_{1-4}alkoxy, $C_{1-2}alkyoxyC_{1-2}$alkoxy, OH, halogen, and 4-6 membered heterocycle containing at least one O or N;

ii) said heterocycle or cycloalkyl is optionally substituted with 1-3 R^e each independently selected from deuterated C_{1-3}alkyl, di(C_{1-3}alkyl)amine, $S(O)_2C_{1-3}$alkyl, halogen, 4-6 membered heterocycle containing one O, C_{1-3}alkyl, C_{0-4}alkylOH, and $C_{1-2}alkylC_{1-3}$alkoxy; and

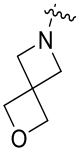
iii) said heteroaryl is optionally substituted with 1-3 R^e each independently selected from C_{1-4}alkyl, CN, CHF_2, cyclopropyl, C_{1-4}alkylOH, C_{2-5}alkyl$(OH)_2$, C_{2-4}alkyl(OH)(methoxy), C_{2-5}alkyl(OH)(C_{1-5}alkoxy)(C_{1-5}alkoxy), $S(O)_2C_{1-3}$alkyl, C_{1-3}alkyl-S(O)(NH)C_{1-3}alkyl, (C_{1-3}alkyl)P(O)(C_{1-3}alkyl)$_2$, and (C_{1-3}alkyl)-(4-6 membered heterocycle containing at least one O or N),wherein said heterocycle is optionally substituted with 1-2 OH or C_{1-3}alkyl.

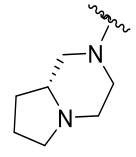
8. The compound or pharmaceutically acceptable salt thereof of claim 7, wherein:

said heteroaryl in subsection iii) is optionally substituted with 1-3 R^e each independently selected from C_{1-4}alkyl, CN, CHF_2, cyclopropyl, C_{1-4}alkylOH, C_{2-4}alkyl(OH)(methoxy), $S(O)_2C_{1-3}$alkyl, C_{1-3}alkyl-S(O)(NH)C_{1-3}alkyl, (C_{1-3}alkyl)P(O)(C_{1-3}alkyl)$_2$, and (C_{1-3}alkyl)-(4-6 membered heterocycle containing at least one O or N),wherein said heterocycle is optionally substituted with 1-2 OH.

9. The compound of any one of clams 1-3, 5 and 6 or pharmaceutically acceptable salt thereof, wherein:

each R^1 is independently selected from halogen, C_{1-3}alkyl, C_{1-4}alkylOH, C_{0-4}alkylC_{1-5}alkoxy, C_{0-4}alkylC_{1-5}haloalkoxy, cyclopropyl, NH_2, NHC_{1-4}alkyl, $N(C_{1-2}$alkyl$)_2$, NH-(5 membered heterocycle containing one O), NH-(5 membered heteroaryl containing two N),



,


, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, and pyrazolyl, wherein:

i) said alkyl or alkoxy is optionally substituted with 1-3 R^e each independently selected from deuterium, C_{1-3}alkyl, C_{1-3}haloalkoxy, deuterated methoxy, OH, C_{1-4}alkoxy, C_{1-2}alkyoxyC_{1-2}alkoxy, halogen and 4-6 membered heterocycle containing at least one O;

ii) said azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, tetrahydrofuran or morpholino is optionally substituted with 1-2 R^e each independently selected from deuterated C_{1-3}alkyl, di(C_{1-3}alkyl)amine, $S(O)_2CH_3$, halogen, C_{0-3}alkylOH, 4-6 membered heterocycle containing one O, C_{1-2}alkyl, C_{1-2}haloalkyl, and C_{1-2}alkylC_{1-3}alkoxy; and

iii) said pyrazolyl is optionally substituted with 1-3 R^e each independently selected from C_{1-4}alkyl, CN, CHF_2, cyclopropyl, C_{0-4}alkylOH, C_{2-5}alkyl$(OH)_2$, C_1-$_4$alkyl(OH)(C_1-C_4alkoxy), C_2-$_5$alkyl(OH)(C_1-$_5$alkoxy)(C_1-$_5$alkoxy), $S(O)_2C_{1-3}$alkyl, C_{1-3}alkyl-S(O)(NH)CH_3, (C_{1-3}alkyl)P(O)(C_{2-3}alkyl)$_2$, and (C_{1-3}alkyl)-(6 membered heterocycle containin at least one O or N), further wherein said 6 membered heterocycle is optionally substituted with 1-2 OH or C_{1-3}alkyl.

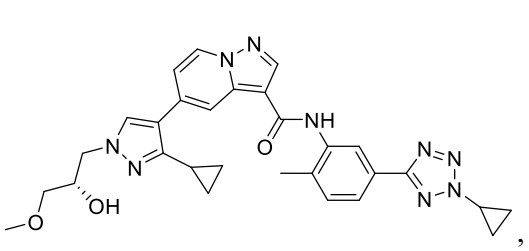
10. The compound or pharmaceutically acceptable salt thereof of claim 9, wherein:

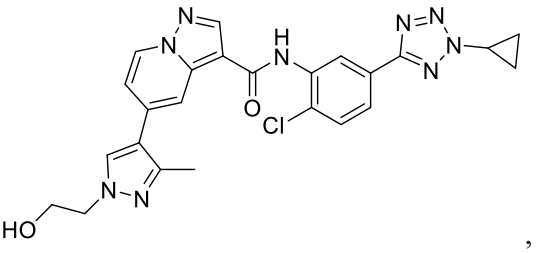
said pyrazolyl in subsection iii) is optionally substituted with 1-3 R^e each independently selected from C_{1-4}alkyl, CN, CHF_2, cyclopropyl, C_{0-4}alkylOH, C_1-$_4$alkyl(OH)(C_1-C_4alkoxy), $S(O)_2C_{1-3}$alkyl, C_{1-3}alkyl-S(O)(NH)CH_3, (C_{1-3}alkyl)P(O)(C_{2-3}alkyl)$_2$, and (C_{1-3}alkyl)-(6 membered heterocycle containin at least one O or N), further wherein said 6 membered heterocycle is optionally substituted with 1-2 OH.

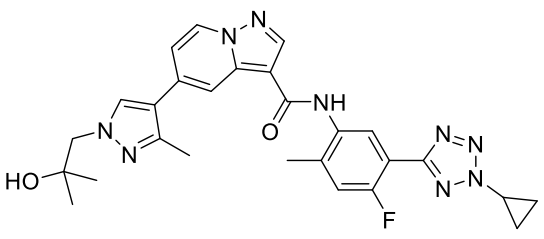
11. The compound of any one of claims 1-10 or pharmaceutically acceptable salt thereof, wherein each R^9 is independently selected from CH_3, Cl, F, CD_3, CN, and cyclopropyl.

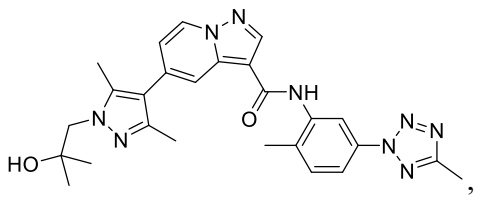
12. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from a compound in Table 1.

13. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

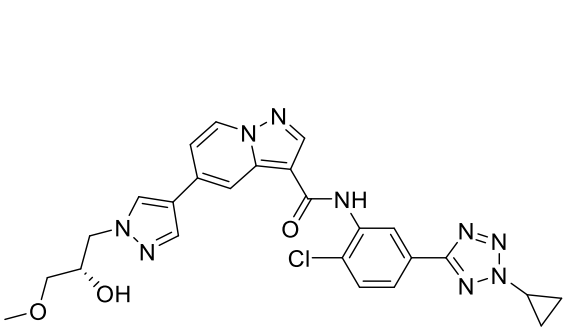
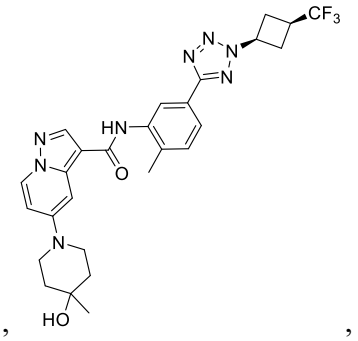
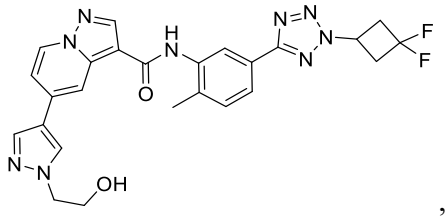
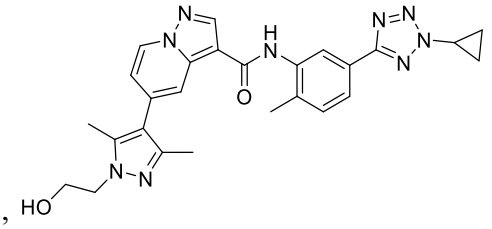
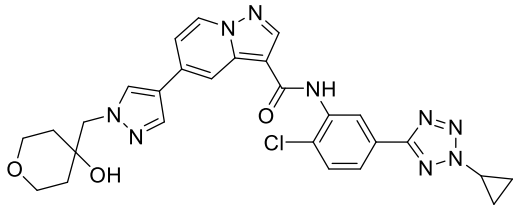
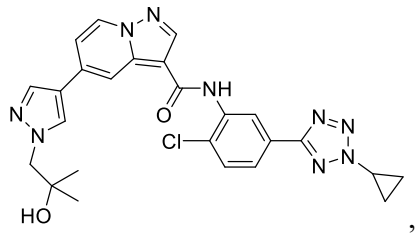


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or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of any one of claims 1-13 or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier or excipient.

15. Use of a compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14 in the manufacture of a medicament for the treatment of a subject suffering from a disease or disorder wherein

(i) the disease or disorder is selected from urticaria, dermatosis, idiopathic anaphylaxis, asthma, hereditary alpha tryptasemia (HAT), neurofibromatosis, idiopathic pulmonary fibrosis, bullous pemphigoid, prurigo nodularis, age-related macular degeneration, allergic conjunctivitis, allergic rhinitis, alpha-1 antitrypsin deficiency, Alzheimer's disease, amyotrophic lateral sclerosis (AML), bronchiectasis, Celiac disease, chronic graft verse host disease, chronic rhinosinusitis with nasal polyps, colorectal cancer, dermatitis herpetiformis, irritable bowel syndrome (IBS), fibromyalgia, fibrosis, food allergies, insulin-dependent

diabetes mellitus, mast cell leukemia, migraine, multiple sclerosis, Parkinson's disease, psoriasis, rheumatoid arthritis, pulmonary arterial hypertension (PAH), inflammatory bowel disease (IBD), scleroderma, dermatosis, dermatitis herpetiformis, melanoma, gastrointestinal stromal tumor, mast cell tumor, anaphylactic syndrome, idiopathic anaphylaxis, eosinophilic esophagitis and mastocytosis;

(ii) the disease or disorder is chronic urticaria; or

(iii) the disease or disorder is chronic spontaneous urticaria (CSU),

optionally wherein the subject is resistant to antihistamine treatment (i.e., the subject remains symptomatic despite antihistamine treatment).

16. A compound of any one of claims 1-13, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 14, for use in therapy.