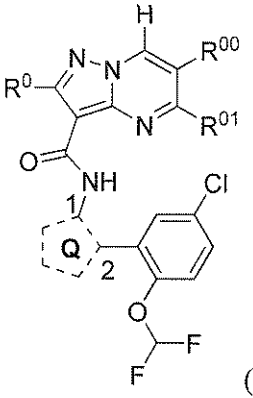
SUMMARY

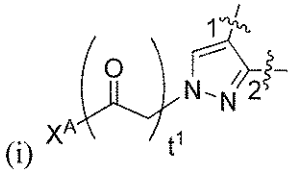
Provided herein are 5-chloro-2-difluoromethoxyphenyl pyrazolopyrimidine compounds that inhibit one or more JAK kinases.

Accordingly, one aspect of the disclosure includes a compound of Formula (00A):

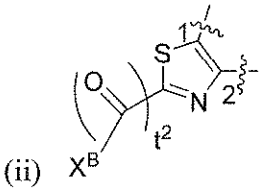


(00A)

and stereoisomers and salts thereof, wherein: R^{00} is H or CH_3; R^{01} is H or NH_2; R^0 is H or NH_2; and Ring Q is either (i) or (ii):



(i)



(ii)

wherein: t^1 and t^2 are each independently 0 or 1; X^A and X^B are independently selected from the group consisting of H, C_1-C_6 alkyl, C_2-C_4 alkenyl, $-NR^aR^b$, C_2-C_5 alkynyl, 3-6-membered cycloalkyl, 6-10 membered aryl, 3-11 membered heterocycloalkyl, 5-6 membered heterocycloalkenyl, and 5-10 membered heteroaryl; wherein when either of X^A and X^B are independently C_1-C_6 alkyl, C_2-C_4 alkenyl, C_2-C_5 alkynyl, 3-6-membered cycloalkyl, 6-10 membered aryl, 3-11 membered heterocycloalkyl, 5-6 membered heterocycloalkenyl, and 5-10 membered heteroaryl, each of X^A and X^B is independently optionally substituted by Y^1, wherein Y^1 is selected from:

(e) -(C_1-C_6 alkylene)-4-6 membered heterocycloalkyl wherein the heterocycloalkyl is optionally substituted by halo, oxo, or C_1-C_6 alkyl;

(f) -(C_1-C_6 alkylene)-O-phenyl wherein the phenyl is optionally substituted by halo, C_1-C_6 alkyl, or -O-phenyl;

(g) –(C_1-C_6 alkyl)3-6 membered cycloalkyl optionally substituted by OH, halo, CN, or C_1-C_6 alkyl optionally substituted by OH or CN;

(h) C_2-C_5 alkenyl;

(i) 4-6 membered heterocycloalkyl optionally substituted by halo,

(j) -(C_1-C_6 alkylene)-3-6 membered cycloalkyl substituted by hydroxymethyl,

(k) phenyl,

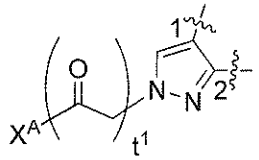
(l) -C(O)(C_1-C_6 alkyl),

(m)-C(O)O(C_1-C_6 alkyl),

(n) -C(O)O(3-6 membered cycloalkyl), and

(o) -C(O)-phenyl,

with the following provisos: when R^0, R^{00}, and R^{01} are each H and Ring Q is



where t^1 is 0, then X^A is not methyl, 2-methylpropan-2-ol, or tetrahydropyranyl; and, in some embodiments, when Ring Q is (i) and t^1 is 0, then X^A cannot be -NR^aR^b.

Further, the disclosure also includes a compound of Formula (00A), further defined as a compound of Formula (0A):

(i) 4-6 membered heterocycloalkyl optionally substituted by halo,

(j) -(C_1-C_6 alkylene)-3-6 membered cycloalkyl substituted by hydroxymethyl,

(k) phenyl,

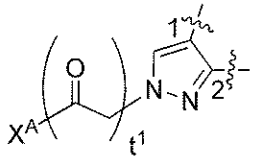
(l) -C(O)(C_1-C_6 alkyl),

(m)-C(O)O(C_1-C_6 alkyl),

(n) -C(O)O(3-6 membered cycloalkyl), and

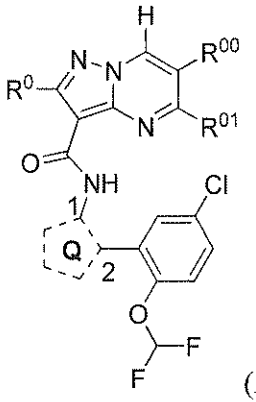
(o) -C(O)-phenyl,

with the following provisos: when R^0, R^{00}, and R^{01} are each H and Ring Q is



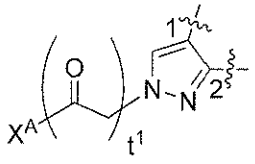
where t^1 is 0, then X^A is not methyl, 2-methylpropan-2-ol, or tetrahydropyranyl; and, in some embodiments, when Ring Q is (i) and t^1 is 0, then X^A cannot be $-NR^aR^b$.

The disclosure also includes a compound of Formula (00A), further defined as a compound of Formula (A):



(A)

and stereoisomers and salts thereof, wherein: R^{00} is H or CH_3; R^{01} is H or NH_2; R^0 is H or NH_2; and Ring Q is either (i) or (ii):



where t^1 is 0, then X^A is not methyl, 2-methylpropan-2-ol, or tetrahydropyranyl; and, in some embodiments, when Ring Q is (i) and t^1 is 0, then X^A cannot be $-NR^aR^b$.

Also provided are pharmaceutical compositions comprising a 5-chloro-2-difluoromethoxyphenyl pyrazolopyrimidine as described herein, such as a compound of Formula (00A) and a pharmaceutically acceptable carrier, dilient or excipient. According to another aspect, there is provided a pharmaceutical composition comprising a compound as described herein and a pharmaceutically acceptable carrier, dilient or excipient.

The present disclosure also provides, in some embodiments, use of a 5-chloro-2-difluoromethoxyphenyl pyrazolopyrimidine compound as described herein, such as a compound of Formula (00A), in therapy, such as in the treatment of an inflammatory disease. Also provided are uses of a 5-chloro-2-difluoromethoxyphenyl pyrazolopyrimidine compound as described herein, such as a compound of Formula (00A), for the preparation of a medicament for the treatment of an inflammatory disease. Also provided is a method of preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a 5-chloro-2-difluoromethoxyphenyl pyrazolopyrimidine compound as described herein, such as a compound of Formula (00A).

According to another aspect, there is provided a compound as described herein for use in therapy.

According to another aspect, there is provided use of a compound as described herein in the preparation of a medicament of the treatment of an inflammatory disease.

According to another aspect, there is provided a compound as described herein for use in the treatment of an inflammatory disease.

According to another aspect, there is provided use of a compound as described herein in the preparation of a medicament for the prevention, treatment or for the severity of a disease or condition responsive to the inhibition of a Janus kinase activity.

DESCRIPTION OF THE DRAWINGS

The foregoing aspects and many of the attendant advantages will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings, where:

Figure 1 depicts a matched pair analysis of certain compounds of the present invention containing either an OMe (**i**) or $OCHF_2$ (**ii**) group at the indicated position.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

22. The compound of claim 1, wherein Ring Q is (i), t^1 is 0 or 1, and R^0, R^{00} and R^{01} are each H.

23. The compound of claim 1, wherein Ring Q is (i), t^1 is 1, and X^A is NR^aR^b, wherein R^a and R^b are each independently H, C_1-C_6 alkyl optionally substituted with 5-6 membered heteroaryl, or 3-6 membered cycloalkyl optionally substituted by OH, halo, CN, or C_1-C_6 alkyl optionally substituted by OH.

24. The compound of claim 1, wherein Ring Q is (i), t^1 is 0, and X^A is C_1-C_6 alkyl or 3-6 membered cycloalkyl, wherein X^A is optionally substituted by $-NR^aR^b$, wherein R^a and R^b are independently H or C_1-C_6 alkyl.

25. The compound of claim 1, selected from Table 1.

26. A pharmaceutical composition comprising a compound of any of claims 1-25 and a pharmaceutically acceptable carrier, diluent or excipient.

27. A compound of any of claims 1-25 for use in therapy.

28. Use of a compound of any of claims 1-25 in the preparation of a medicament for the treatment of an inflammatory disease.

29. A compound of any of claims 1-25 for use in the treatment of an inflammatory disease.

30. The use or compound of any of claims 28-29, wherein the inflammatory disease is asthma.

31. Use of a compound of any of claims 1-25 in the preparation of a medicament for the prevention, treatment or for the severity of a disease or condition responsive to the inhibition of a Janus kinase activity.

32. The use of claim 31, wherein the disease or condition is asthma.

33. The use of claim 31, wherein the Janus kinase is JAK1.