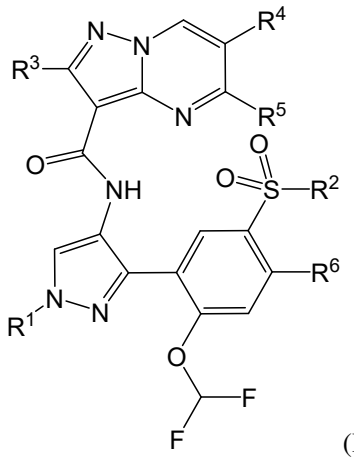
benefit, in conditions responsive to the inhibition of JAK1. Additionally there is currently a need for potent JAK1 inhibitors that possess other properties (e.g., melting point, pK, solubility, etc.) necessary for formulation and administration by inhalation. Such compounds would be particularly useful for treating conditions such as, for example, asthma.

There accordingly exists a need in the art for additional or alternative treatments of conditions mediated by JAK kinases, such as those described above. There is in particular a need for JAK1 and JAK2 kinase inhibitors usable for inhaled delivery in the treatment of airway inflammation indications such as asthma.

SUMMARY ~~OF THE INVENTION~~

Provided herein are pyrazolopyrimidines that inhibit JAK kinases, such as selected from a compound of Formula (I) a stereoisomer or salt thereof, such as a pharmaceutically acceptable salt thereof. The JAK kinase may be JAK1, JAK2, or both.

One ~~embodiment~~example provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein:

R^1 is: C_{1-6}alkyl; cyano-C_{1-6}alkyl; C_{1-6}alkoxy-(CO)-; -$(CHR^a)_m$-NR^bR^c; or -$(CHR^a)_n$-het^1;

R^2 is: C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; halo-C_{1-6}alkyl; C_{1-6}alkoxy-C_{1-6}alkyl; C_{3-6}cycloalkyl; -$(CHR^a)_p$-NR^bR^c; het^2; -$(CHR^a)_q$-het^3; or phenyl which may be unsubstituted or substituted once or twice with R^d;

R^3 is: hydrogen; amino; or C_{1-6}alkyl;

R^4 is: hydrogen; or C_{1-6}alkyl;

R^5 is: hydrogen; or C_{1-6}alkyl;

R^6 is: hydrogen; C_{1-6}alkyl; or R^2 and R^6 together with the atoms to which they are attached may form a six membered ring;

m is from 2 to 3;

n is from 0 to 2;

p is from 0 to 2;

each R^a is independently: hydrogen; or C_{1-6}alkyl;

each R^b is independently: hydrogen; or C_{1-6}alkyl;

each R^c is independently: hydrogen; or C_{1-6}alkyl;

het^1 is: tetrahydrofuranyl; azetidinyl; or pyrrolidinyl, each of which may be unsubstituted or substituted once or twice with R^e;

het^2 is: pyridinyl; pyrimidinyl; pyrazolyl; imidazolyl; or isoquinolinyl which may be partially saturated; each of which may be unsubstituted or substituted once or twice with R^f;

het^3 is: azetidinyl; pyrrolidinyl; oxetanyl; or piperidinyl; each of which may be unsubstituted or substituted once with R^g;

each R^d is independently: C_{1-6}alkyl; hydroxy; C_{1-6}alkoxy-C_{1-6}alkyl; $-(CHR^a)_q-NR^bR^c$; or phenyl;

each R^e is independently: C_{1-6}alkyl; or oxo;

each R^f is independently: C_{1-6}alkyl; hydroxy-C_{1-6}alkyl; oxo; $-(CHR^a)_r-NR^bR^c$; $-(CHR^a)_s-het^4$;

each R^g is independently: C_{1-6}alkyl; or acetyl;

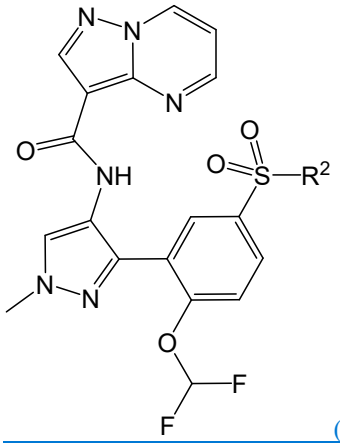
q is from 1 to 2;

r is from 2 to 3;

s is from 2 to 3; and

het^4 is: azetidin-1-yl; 1-methyl-azetidin-3-yl; quinuclidinyl; 1-methyl-pyrrolidin-2-yl; or 4-methylpiperazin-1-yl.

In one aspect, the present disclosure provides a compound of formula (III)



(III)

wherein R^2 is hydroxy-C_{1-6}alkyl,

or a stereoisomer or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition comprises microparticles of the compound suitable for inhaled delivery. Also provided is a pharmaceutical composition comprising a JAK inhibitor as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, dilient or excipient.

In one aspect, the present disclosure provides a compound disclosed herein or a stereoismer or pharmaceutically acceptable salt thereof for use in the treatment of an inflammatory disease. Also provided is the use of a JAK inhibitor as described herein, or a pharmaceutically acceptable salt thereof in therapy, such as in the treatment of an inflammatory disease (e.g., asthma). In another aspect, the present disclosure provides use of a compound disclosed herein or a stereoismer or pharmaceutically acceptable salt thereof for preparation of a medicament for treatment of an inflammatory disease. In yet another aspect, the present disclosure provides use of a compound disclosed herein or a stereoismer or pharmaceutically acceptable salt thereof for preparation of a medicament for treatment of an inflammatory disease, wherein the inflammatory disease is asthma. Also provided is the use of a JAK inhibitor as described herein or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of an inflammatory disease. In one aspect., the present disclosure provides use of a compound disclosed herein, or a stereoisomer or pharmaceutically acceptable salt thereof in the manufacture of a medicament for preventing, treating or lessening the severity of a disease or condition responsive to the inhibition of a Janus kinase activity in a patient. 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 JAK inhibitor as described herein or a pharmaceutically acceptable salt thereof.

The most validated cytokines in asthma (IL-4, IL-5, IL-9, IL-13, and TSLP) all signal through JAK1 and/or JAK2. The compounds of the ~~invention~~disclosure are active for both JAK1 and JAK2. Certain of these compounds optimally have well-balanced co-activity for both JAK1 and JAK2, or have slightly higher affinity for JAK1 over JAK2, rather than having a much greater activity for one of these kinases over the other. The subject compounds also have good selectivity against off-target kinases such as LRRK2, which has been associated with pulmonary toxicity.

While many compounds may exhibit high affinity for both JAK1 and JAK2 in simple biochemical assays, not all such compounds are effective at mediating the relevant cytokines associated with JAK1 and JAK2. Certain compounds of the ~~invention~~disclosure, in addition to being active for both JAK1 and JAK2, are also shown in cell-based assays to be effective at mediation of asthma-relevant cytokines associated with JAK1 and JAK2.

Compounds of the ~~invention~~disclosure also exhibit favorable pharmacokinetic (PK) properties in lung tissue and are useful for inhaled therapies. When dosed via the inhaled route using techniques such as dry powder inhalation (DPI) or intranasal (IN) delivery, certain compounds unexpectedly show sustained retention within the lung tissue, with much lower concentrations in systemic circulation. Such improved PK properties can advantageously result in smaller dosages and less frequent dosing requirements for effective therapies. Certain compounds exhibit unexpected improved solubility, again providing inproved efficacy in lung. Certain compounds of the ~~invention~~disclosure also exhibit unexpected reduction in cytotoxicity in comparison to other JAK inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

"Halogen" or "halo" refers to F, Cl, Br or I. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl, wherein one or more halogens replace a hydrogen(s) of an alkyl group.

The term "alkyl" refers to a saturated linear or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted. In one example, the alkyl radical is one to eighteen carbon atoms (C_1-C_{18}). In other examples, the alkyl radical is C_0-C_6, C_0-C_5, C_0-C_3, C_1-C_{12}, C_1-C_{10}, C_1-C_8, C_1-C_6, C_1-C_5, C_1-C_4, or C_1-C_3. C_0 alkyl refers to a bond. Examples of alkyl groups include methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -