AZETIDINYL PHENYL, PYRIDYL OR PYRAZINYL CARBOXAMIDE DERIVATIVES AS JAK INHIBITORS

This application claims the benefit of priority of U.S. Provisional Application Nos. 61/498,942, filed June 20, 2011, and 61/591,094, filed January 26, 2012, each of which is incorporated herein by reference in its entirety.

TECHNICAL FIELD

The present invention provides azetidinyl phenyl, pyridyl, or pyrazinyl carboxamide derivatives, as well as their compositions and methods of use that inhibit the activity of Janus kinases (JAKs) and are useful in the treatment of diseases related to the activity of JAK including, for example, inflammatory disorders, autoimmune disorders, cancer, and other diseases.

BACKGROUND

Protein kinases (PKs) regulate diverse biological processes including cell growth, survival, differentiation, organ formation, morphogenesis, neovascularization, tissue repair, and regeneration, among others. Protein kinases also play specialized roles in a host of human diseases including cancer. Cytokines, low-molecular weight polypeptides or glycoproteins, regulate many pathways involved in the host inflammatory response to sepsis. Cytokines influence cell differentiation, proliferation and activation, and can modulate both pro-inflammatory and anti-inflammatory responses to allow the host to react appropriately to pathogens. Signaling of a wide range of cytokines involves the Janus kinase family (JAKs) of protein tyrosine kinases and Signal Transducers and Activators of Transcription (STATs). There are four known mammalian JAKs: JAK1 (Janus kinase-1), JAK2, JAK3 (also known as Janus kinase, leukocyte; JAKL; and L-JAK), and TYK2 (protein-tyrosine kinase 2).

Cytokine-stimulated immune and inflammatory responses contribute to pathogenesis of diseases: pathologies such as severe combined immunodeficiency (SCID) arise from suppression of the immune system, while a hyperactive or inappropriate immune/inflammatory response contributes to the pathology of autoimmune diseases (*e.g.*, asthma, systemic lupus erythematosus, thyroiditis,

myocarditis), and illnesses such as scleroderma and osteoarthritis (Ortmann, R. A., T. Cheng, *et al.* (2000) *Arthritis Res* 2(1): 16-32).

Deficiencies in expression of JAKs are associated with many disease states. For example, JAK1-/- mice are runted at birth, fail to nurse, and die perinatally (Rodig, S. J., M. A. Meraz, *et al.* (1998) *Cell* 93(3): 373-83). JAK2-/- mouse embryos are anemic and die around day 12.5 postcoitum due to the absence of definitive erythropoiesis.

The JAK/STAT pathway, and in particular all four JAKs, are believed to play a role in the pathogenesis of asthmatic response, chronic obstructive pulmonary disease, bronchitis, and other related inflammatory diseases of the lower respiratory tract. Multiple cytokines that signal through JAKs have been linked to inflammatory diseases/conditions of the upper respiratory tract, such as those affecting the nose and sinuses (*e.g.*, rhinitis and sinusitis) whether classically allergic reactions or not. The JAK/STAT pathway has also been implicated in inflammatory diseases/conditions of the eye and chronic allergic responses.

Activation of JAK/STAT in cancers may occur by cytokine stimulation (*e.g.* IL-6 or GM-CSF) or by a reduction in the endogenous suppressors of JAK signaling such as SOCS (suppressor or cytokine signaling) or PIAS (protein inhibitor of activated STAT) (Boudny, V., and Kovarik, J., *Neoplasm.* 49:349-355, 2002). Activation of STAT signaling, as well as other pathways downstream of JAKs (*e.g.*, Akt), has been correlated with poor prognosis in many cancer types (Bowman, T., *et al. Oncogene* 19:2474-2488, 2000). Elevated levels of circulating cytokines that signal through JAK/STAT play a causal role in cachexia and/or chronic fatigue. As such, JAK inhibition may be beneficial to cancer patients for reasons that extend beyond potential anti-tumor activity.

JAK2 tyrosine kinase can be beneficial for patients with myeloproliferative disorders, *e.g.*, polycythemia vera (PV), essential thrombocythemia (ET), myeloid metaplasia with myelofibrosis (MMM) (Levin, *et al., Cancer Cell*, vol. 7, 2005: 387-397). Inhibition of the JAK2V617F kinase decreases proliferation of hematopoietic cells, suggesting JAK2 as a potential target for pharmacologic inhibition in patients with PV, ET, and MMM.

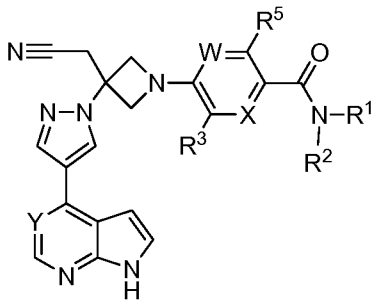
Inhibition of the JAKs may benefit patients suffering from skin immune disorders such as psoriasis, and skin sensitization. The maintenance of psoriasis is believed to depend on a number of inflammatory cytokines in addition to various

chemokines and growth factors (JCI, 113:1664-1675), many of which signal through JAKs (*Adv Pharmacol.* 2000;47:113-74).

Thus, new or improved agents which inhibit kinases such as JAKs are continually needed for developing new and more effective pharmaceuticals that are aimed at augmentation or suppression of the immune and inflammatory pathways (such as immunosuppressive agents for organ transplants), as well as agents for the prevention and treatment of autoimmune diseases, diseases involving a hyperactive inflammatory response (*e.g.*, eczema), allergies, cancer (*e.g.*, prostate, leukemia, multiple myeloma), and some immune reactions (*e.g.*, skin rash or contact dermatitis or diarrhea) caused by other therapeutics. The compounds of the invention, as well as its compositions and methods described herein are directed toward these needs and other ends.

SUMMARY

The present invention provides, *inter alia*, compounds of Formula I:



I

or pharmaceutically acceptable salts thereof; wherein the variables are defined *infra*.

The present invention further provides compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention further provides methods of modulating an activity of JAK1 comprising contacting JAK1 with a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating a disease or a disorder associated with abnormal kinase expression or activity in a patient by administering to a patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention further provides methods of treating an autoimmune disease, a cancer, a myeloproliferative disorder, an inflammatory disease, a bone resorption disease, or organ transplant rejection in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

The present invention also provides compounds of Formula I, or pharmaceutically acceptable salts thereof, as described herein for use in treatment of autoimmune diseases, cancer, myeloproliferative disorders, inflammatory diseases, a bone resorption disease, or organ transplant rejection.

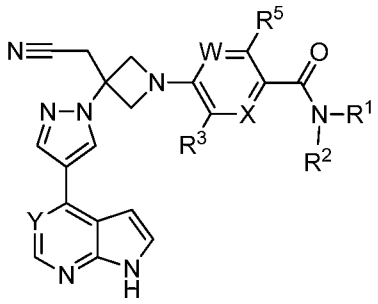
The present invention further provides compounds of Formula I as described herein, or pharmaceutically acceptable salts thereof, for use in modulating JAK1.

The present invention also provides uses of compounds of Formula I as described herein, or pharmaceutically acceptable salts thereof, for the preparation of medicaments for use in methods of modulating JAK1.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and claims.

DETAILED DESCRIPTION

The present invention provides, *inter alia*, a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl; wherein

said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, and 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, C_{1-3} alkyl, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -C(O)N(C_{1-3} alkyl)$_2$, -C(O)NH(C_{1-3} alkyl), -C(O)NH_2, -C(O)O(C_{1-3} alkyl), -S(O)$_2$(C_{1-3} alkyl), -S(O)$_2$(C_{3-6} cycloalkyl), -C(O)(C_{3-6} cycloalkyl), and -C(O)(C_{1-3} alkyl);

R^2 is H or C_{1-3} alkyl; wherein said C_{1-3} alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, NH_2, -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$; or

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered heterocycloalkyl ring; which is optionally substituted with 1, 2, or 3 substitutents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and -CH_2CN;

R^3 is H, F, Cl, -CN, C_{1-3} alkyl, -OCF_3, -CF_3, or -O(C_{1-3} alkyl);

R^4 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^5 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^6 is H, F, Cl, -CN, or C_{1-3} alkyl; and

R^7 is H, F, Cl, -CN, C_{1-3} alkyl, -CH_2CN, -C(O)N(C_{1-3} alkyl)$_2$, -C(O)NH(C_{1-3} alkyl), or -C(O)NH_2.

In some embodiments, Y is N.

In some embodiments, Y is CR^7.

In some embodiments, R^7 is H.

In some embodiments, X is N.

In some embodiments, X is CR^4.

In some embodiments, R^4 is H or F.

In some embodiments, W is N.

In some embodiments, W is CR^6.

In some embodiments, R^6 is H, F, or Cl.

In some embodiments, R^5 is H or F.

In some embodiments, R^6 is H or F.

In some embodiments, R^6 is H.

In some embodiments, R^2 is H or methyl.

In some embodiments, R^2 is H.

In some embodiments, R^2 is methyl.

In some embodiments, R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, and 5-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro,
-CF_3, and methyl.

In some embodiments, R^1 is isopropyl, ethyl, 1-methylpropyl, 2,2,2-trifluoro-1-methylethyl, 1-cyclopropylethyl, 1-cyclohexylethyl, cyclopropyl, 1-trifluoromethylcyclopropyl, 3,3-difluorocyclobutyl, 1-(1-methylpiperidin-4-yl)ethyl, 1-cyclopropyl-2,2,2-trifluoroethyl, 2,2,2-trifluoroethyl, or 2,2-difluoroethyl.

In some embodiments, R^1 is isopropyl, ethyl, 1-methylpropyl, 2,2,2-trifluoro-1-methylethyl, 1-cyclopropylethyl, 1-cyclohexylethyl, cyclopropyl, 1-trifluoromethylcyclopropyl, 3,3-difluorocyclobutyl, or 1-(1-methylpiperidin-4-yl)ethyl.

In some embodiments, R^1 is isopropyl.

In some embodiments, R^1 is ethyl.

In some embodiments, R^1 is 1-methylpropyl.

In some embodiments, R^1 is 2,2,2-trifluoro-1-methylethyl.

In some embodiments, R^1 is 1-trifluoromethylcyclopropyl.

In some embodiments, R^1 is 1-cyclopropyl-2,2,2-trifluoroethyl.

In some embodiments, R^1 is 2,2,2-trifluoroethyl.

In some embodiments, R^1 is 2,2-difluoroethyl.

In one embodiment (a):

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl; wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, C_{1-3} alkyl, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -

$C(O)N(C_{1-3}\,alkyl)_2$, $-C(O)NH(C_{1-3}\,alkyl)$, $-C(O)NH_2$, $-C(O)O(C_{1-3}\,alkyl)$, $-S(O)_2(C_{1-3}$ alkyl), $-S(O)_2(C_{3-6}\,cycloalkyl)$, $-C(O)(C_{3-6}\,cycloalkyl)$, and $-C(O)(C_{1-3}\,alkyl)$;

R^2 is H or C_{1-3} alkyl; wherein said C_{1-3} alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, -OH, $-O(C_{1-3}\,alkyl)$, -CN, $-CF_3$, NH_2, $-NH(C_{1-3}\,alkyl)$, and $-N(C_{1-3}\,alkyl)_2$; or

R^3 is H, F, Cl, -CN, C_{1-3} alkyl, $-OCF_3$, $-CF_3$, or $-O(C_{1-3}\,alkyl)$;

R^4 is H, F, Cl, -CN, C_{1-3} alkyl, or $-O(C_{1-3}\,alkyl)$;

R^5 is H, F, Cl, -CN, C_{1-3} alkyl, or $-O(C_{1-3}\,alkyl)$;

R^6 is H, F, Cl, -CN, or C_{1-3} alkyl; and

R^7 is H, F, Cl, -CN, C_{1-3} alkyl, or $-CH_2CN$.

In another embodiment (b):

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, $-O(C_{1-3}\,alkyl)$, -CN, $-CF_3$, C_{1-3} alkyl, $-NH_2$, $-NH(C_{1-3}\,alkyl)$, and $-N(C_{1-3}\,alkyl)_2$;

R^2 is H or methyl;

R^3 is H, F, Cl, or methyl;

R^4 is H, F, Cl, or methyl;

R^5 is H, F, Cl, or methyl;

R^6 is H, F, Cl, or methyl; and

R^7 is H.

In another embodiment (c):

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally

substituted with 1, 2, or 3 substituents independently selected from fluoro, -CF_3, and methyl;

R^2 is H or methyl;

R^3 is H, F, or Cl;

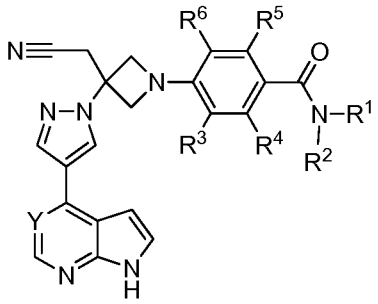
R^4 is H or F;

R^5 is H or F;

R^6 is H; and

R^7 is H.

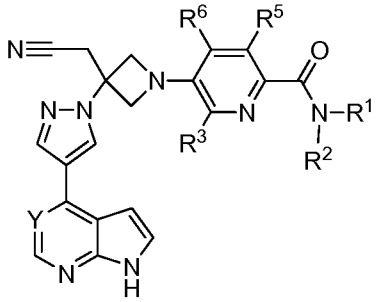
In some embodiments, the compound is a compound of Formula II:



II

or a pharmaceutically acceptable salt thereof.

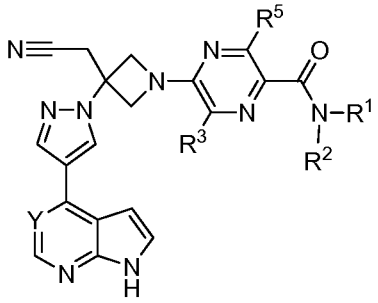
In some embodiments, the compound is a compound of Formula III:



III

or a pharmaceutically acceptable salt thereof.

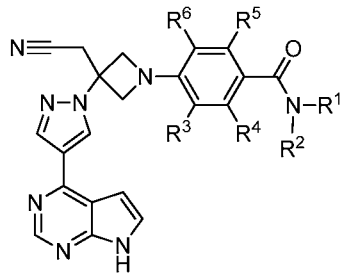
In some embodiments, the compound is a compound of Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

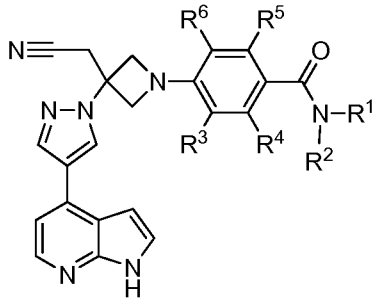
In some embodiments, the compound is a compound of Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

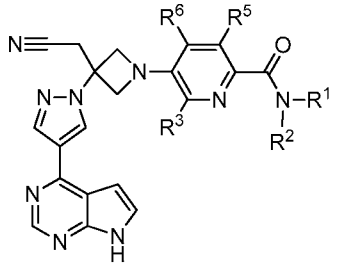
In some embodiments, the compound is a compound of Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof.

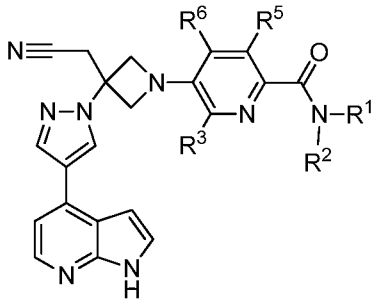
In some embodiments, the compound is a compound of Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

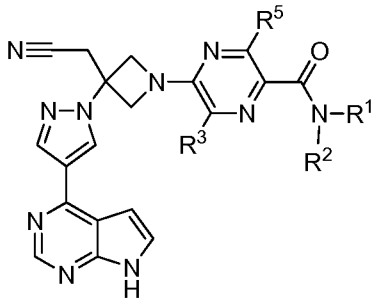
In some embodiments, the compound is a compound of Formula IIIb:



IIIb

or a pharmaceutically acceptable salt thereof.

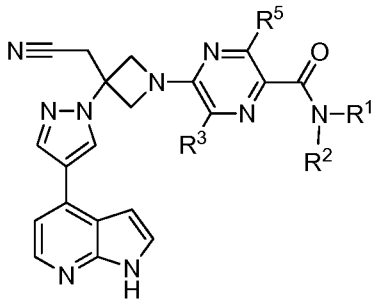
In some embodiments, the compound is a compound of Formula IVa:



IVa

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a compound of Formula IVb:



IVb

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has Formula II, wherein Y, R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula III, wherein Y, R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula IV, wherein Y, R^1, R^2, R^3, and R^5 are defined as in embodiment (a).

In some embodiments, the compound has Formula II, wherein Y, R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula III, wherein Y, R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula IV, wherein Y, R^1, R^2, R^3, and R^5 are defined as in embodiment (b).

In some embodiments, the compound has Formula II, wherein Y, R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula III, wherein Y, R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula IV, wherein Y, R^1, R^2, R^3, and R^5 are defined as in embodiment (c).

In some embodiments, the compound has Formula IIa, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula IIa, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula IIa, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula IIIa, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula IIIa, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula IIIa, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (a).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (b).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (c).

In some embodiments, the compound has Formula IIb, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula IIb, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula IIb, wherein R^1, R^2, R^3, R^4, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula IIIb, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (a).

In some embodiments, the compound has Formula IIIb, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (b).

In some embodiments, the compound has Formula IIIb, wherein R^1, R^2, R^3, R^5, R^6 are defined as in embodiment (c).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (a).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (b).

In some embodiments, the compound has Formula IVa, wherein R^1, R^2, R^3, and R^5 are defined as in embodiment (c).

In some embodiments, the compound is selected from:

4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]-3-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-cyclopropyl-3-fluoro-N-methylbenzamide;

5-Chloro-4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-isopropylbenzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(3,3-difluorocyclobutyl)pyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclohexylethyl]-2-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(1-methylpiperidin-4-yl)ethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide;

5-Chloro-4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-N-[(1*R*)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-ethylpyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-methylpropyl]benzamide; and

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoro-1-methylethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is selected from:

4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2-difluoroethyl)-2,5-difluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2-fluorobenzamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide;

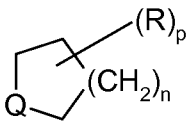
5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide; or a pharmaceutically acceptable salt thereof.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C_{1-6} alkyl" is specifically intended to individually disclose methyl, ethyl, C_3 alkyl, C_4 alkyl, C_5 alkyl, and C_6 alkyl.

The term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

For compounds of the invention in which a variable appears more than once, each variable can be a different moiety independently selected from the group defining the variable. For example, where a structure is described having two R groups that are simultaneously present on the same compound, the two R groups can represent different moieties independently selected from the group defined for R. In another example, when an optionally multiple substituent is designated in the form:



then it is to be understood that substituent R can occur p number of times on the ring, and R can be a different moiety at each occurrence. It is to be understood that each R group may replace any hydrogen atom attached to a ring atom, including one or both of the $(CH_2)_n$ hydrogen atoms. Further, in the above example, should the variable Q be defined to include hydrogens, such as when Q is said to be CH_2, NH, etc., any

floating substituent such as R in the above example, can replace a hydrogen of the Q variable as well as a hydrogen in any other non-variable component of the ring.

As used herein, the phrase "optionally substituted" means unsubstituted or substituted. As used herein, the term "substituted" means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

As used herein, the term "C_{n-m} alkyl", employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbon atoms. In some embodiments, the alkyl group contains 1 to 6, 1 to 4 or 1 to 3 carbon atoms. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, 2-methyl-1-butyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like.

As used herein, "halo" or "halogen", employed alone or in combination with other terms, includes fluoro, chloro, bromo, and iodo.

As used herein, the term "C_{n-m} haloalkyl", employed alone or in combination with other terms, refers to an C_{n-m} alkyl group having up to {2(n to m)+1} halogen atoms which may either be the same or different. In some embodiments, the halogen atoms are fluoro atoms. In some embodiments, the alkyl group has 1 to 6 or 1 to 4 carbon atoms. Example haloalkyl groups include CF_3, C_2F_5, CHF_2, CCl_3, $CHCl_2$, C_2Cl_5, and the like. In some embodiments, the haloalkyl group is a fluoroalkyl group.

As used herein, the term "C_{n-m} cycloalkyl", employed alone or in combination with other terms, refers to a non-aromatic cyclic hydrocarbon including cyclized alkyl and alkenyl groups, and which has n to m ring member carbon atoms. Cycloalkyl groups can include mono- or bicyclic (e.g., having two fused or bridged rings) ring systems. One or more ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo. Cycloalkyl groups also include cycloalkylidenes. In some embodiments, the cycloalkyl group has 3, 4, 5, or 6 ring members. In some embodiments, the cycloalkyl group has 3 to 6 ring members, 3 to 5 ring members, or 3 to 4 ring members. In some embodiments, the cycloalkyl group is monocyclic. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a C_{3-6} monocyclic cycloalkyl group. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,

cyclopentenyl, cyclohexenyl, cyclohexadienyl, norbornyl, norpinyl, bicyclo[2.1.1]hexanyl, bicyclo[1.1.1]pentanyl, and the like.

As used herein, the term "C_{n-m} cycloalkyl-C_{o-p} alkyl", employed alone or in combination with other terms, refers to a group of formula -alkylene-cycloalkyl, wherein the cycloalkyl portion has n to m carbon atoms and the alkylene portion has o to p carbon atoms. In some embodiments, the alkylene portion has 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkylene portion is methylene or ethylene. In some embodiments, the alkylene portion is methylene. In some embodiments, the cycloalkyl portion has 3 to 6 ring members, 3 to 5 ring members, 3 to 4 ring members, or 3 ring members. In some embodiments, the cycloalkyl group is monocyclic or bicyclic. In some embodiments, the cycloalkyl portion is monocyclic. In some embodiments, the cycloalkyl portion is a C_{3-6} monocyclic cycloalkyl group.

As used herein, the term "4-6 membered heterocycloalkyl", employed alone or in combination with other terms, refers to non-aromatic ring or ring system, which may optionally contain one or more alkenylene groups as part of the ring structure, which has at least one heteroatom ring member independently selected from nitrogen, sulfur oxygen and phosphorus, and which has 4, 5, or 6 ring members. Heterocycloalkyl groups can include mono- or bicyclic (e.g., having two fused or bridged rings) ring systems. In some embodiments, the heterocycloalkyl group is a monocyclic group having 1, 2, or 3 hetereoatoms independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heterocycloalkyl group is a 4- to 6-membered ring, a 5- to 6-membered ring, a 6-membered ring, a 5-membered ring, or a 4-membered ring. One or more carbon atoms or hetereoatoms in the ring(s) of the heterocycloalkyl group can be oxidized to form a carbonyl, an N-oxide, or a sulfonyl group (or other oxidized linkage), or a nitrogen atom can be quaternized. Examples of heterocycloalkyl groups include azetidine, pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, and pyran. In some embodiments, the 4-6 membered heterocycloalkyl is azetidine, pyrrolidine, or piperidine.

As used herein, the term "4- 6 membered heterocycloalkyl-C_{n-m} alkyl", employed alone or in combination with other terms, refers to a group of formula -alkylene-heterocycloalkyl, wherein the heterocycloalkyl portion has 4, 5, or 6 ring members and the alkylene portion has n to m carbon atoms. In some embodiments, the alkylene portion has 1 to 3, 1 to 2, or 1 carbon atom(s). In some embodiments, the alkylene portion is methylene. In some embodiments, the heterocycloalkyl portion

has 4 to 6 ring members, 5 to 6 ring members, or 5 ring members. In some embodiments, the heterocycloalkyl group is monocyclic or bicyclic. In some embodiments, the heterocycloalkyl portion is monocyclic. In some embodiments, the heterocycloalkyl portion is a 4-6 membered monocyclic heterocycloalkyl group.

As used herein, the appearance of the term "bicyclic" before the name of a moiety indicates that the moiety has two fused rings.

As used herein, the appearance of the term "monocyclic" before the name of a moiety indicates that the moiety has a single ring.

The compounds described herein can be asymmetric (*e.g.*, having one or more stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms.

Resolution of racemic mixtures of compounds can be carried out by any of numerous methods known in the art. An example method includes fractional recrystallizaion using a chiral resolving acid which is an optically active, salt-forming organic acid. Suitable resolving agents for fractional recrystallization methods are, for example, optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various optically active camphorsulfonic acids such as β-camphorsulfonic acid. Other resolving agents suitable for fractional crystallization methods include stereoisomerically pure forms of α-methylbenzylamine (*e.g.*, *S* and *R* forms, or diastereomerically pure forms), 2-phenylglycinol, norephedrine, ephedrine, N-methylephedrine, cyclohexylethylamine, 1,2-diaminocyclohexane, and the like.

Resolution of racemic mixtures can also be carried out by elution on a column packed with an optically active resolving agent (*e.g.*, dinitrobenzoylphenylglycine). Suitable elution solvent composition can be determined by one skilled in the art.

Compounds of the invention also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. In some embodiments, 1, 2, or 3 CH_2 groups in the azetidine ring of Formula I are replaced by a CHD or CD_2 group. In some embodiments, 1, 2, or 3 CH_2 or CH groups in the piperidine ring of Formula I are replaced by a CHD, CD_2 or CD group, respectively. In some embodiments, 1, 2, 3, 4, or 5 CH_2 or CH groups in the piperidine ring of Formula I are replaced by a CHD, CD_2 or CD group, respectively.

The term, "compound," as used herein is meant to include all stereoisomers, geometric iosomers, tautomers, and isotopes of the structures depicted.
All compounds, and pharmaceutically acceptable salts thereof, can be found together with other substances such as water and solvents (e.g., hydrates and solvates) or can be isolated.

In some embodiments, the compounds of the invention, or salts thereof, are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The expressions, "ambient temperature" and "room temperature," as used herein, are understood in the art, and refer generally to a temperature, *e.g.* a reaction temperature, that is about the temperature of the room in which the reaction is carried out, for example, a temperature from about 20 °C to about 30 °C.

The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present invention include the non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, alcohols (e.g., methanol, ethanol, iso-propanol, or butanol) or acetonitrile (ACN) are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science*, 66, 2 (1977), each of which is incorporated herein by reference in its entirety. In some embodiments, the compounds described herein include the N-oxide forms.

Synthesis

Compounds of the invention, including salts and N-oxides thereof, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes, such as those in the Schemes below.

The reactions for preparing compounds of the invention can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, *e.g.*, temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

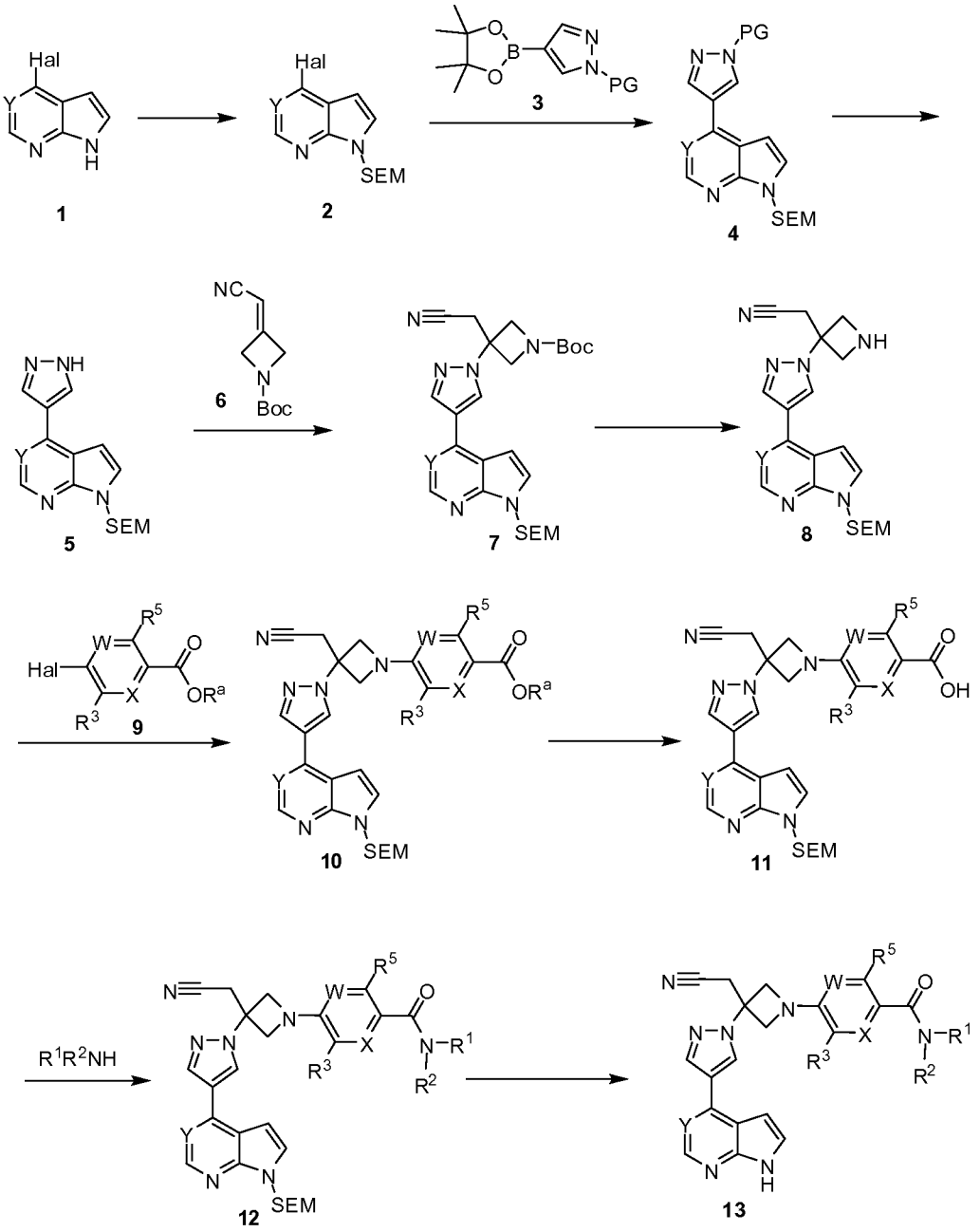
Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, Protective Groups in Organic Synthesis, 4th ed., John Wiley & Sons: New Jersey, (2007), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

A series of arylamide derivatives **13** (Y can be N, CH or CR^7; W can be N or CR^6, and X can be N or CR^4) can be prepared according to the procedure outlined in Scheme 1. Protected bicyclo-hetero compound **2** can be achieved by reaction of the corresponding bicyclo-hetero compound **1** with (2-(chloromethoxy)ethyl)trimethylsilane (SEMCl) in the presence of the suitable base such as NaH in DMF. Suzuki coupling of the bicyclo-hetero compound **2** with suitable boronic acid **3** produces the corresponding compound **4**. The protecting group (PG) in compound **4** can be removed to give the compound **5** by hydrogenation in the presence of palladium on carbon in the case of PG = Cbz or in the case of PG = Boc by treatment with acid such as, but not limited to, trifluoroacetic acid (TFA) or HCl in a suitable solvent such as, but not limited to, dichloromethane (DCM), methanol, dioxane, or combination of two solvents, or with base such as sodium carbonate or potassium carbonate in hot methanol. Michael addition of **5** with α,β-

unsaturated nitrile **6** can afford the adduct **7**. Removal of the Boc group in **7** yields the amine derivative **8** which can be converted to the corresponding aryl ester **10** by reaction with halo-substituted arylacid ester **9** in the presence of the suitable catalyst such as, but not limited to, BINAP [2,2'-bis(diphenylphosphino)-1,1'binaphthalene], Tol-BINAP [2,2'-bis(di-p-tolylphosphino)-1,1'binaphthalene], Xanthpos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene]. The aryl ester **10** can be hydrolyzed to the corresponding acid **11** by using an alkali such as lithium hydroxide, sodium hydroxide or potassium hydroxide. Coupling of the acid **11** with an appropriate amine can yield an arylamide **12** by using a coupling reagent such as but not limited to, BOP, PyOP, HATU, HBTU, EDC, or CDI. Removal of the protecting group SEM in **12** to afford the arylamide derivative **13** can be achieved by treatment with an acid such as BF_3, or TFA, and following by treatment with an amine such as ethylenediamine or ammonia.

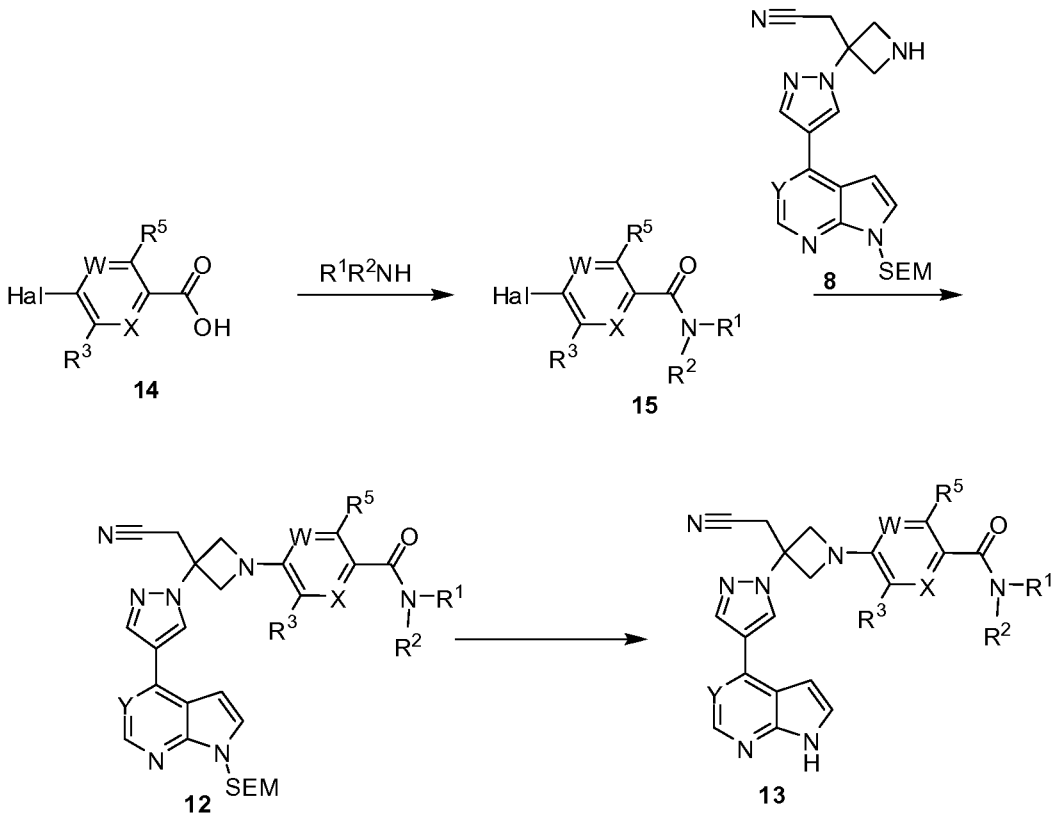
Scheme 1



Alternatively, the arylamide derivatives **13** can be prepared according to the procedure outlined in Scheme 2. An aromatic acid **14** can be conveniently converted to the corresponding amide **15** by using the amide coupling reagent such as BOP, PyOP, HATU, HBTU, EDC, or CDI. Aromatic amination of **8** with the amide **15** to produce **12** can be archived similar to those described above in the presence of the suitable catalyst such as, but not limited to, BINAP [2,2'-bis(diphenylphosphino)-

1,1'-binaphthalene], Tol-BINAP [2,2'-bis(di-p-tolylphosphino)-1,1'binaphthalene], Xantphos [4,5-bis(diphenylphosphino)-9,9-dimethylxanthene]. Removal of the protecting group SEM in **12** can afford the arylamide **13** as described above.

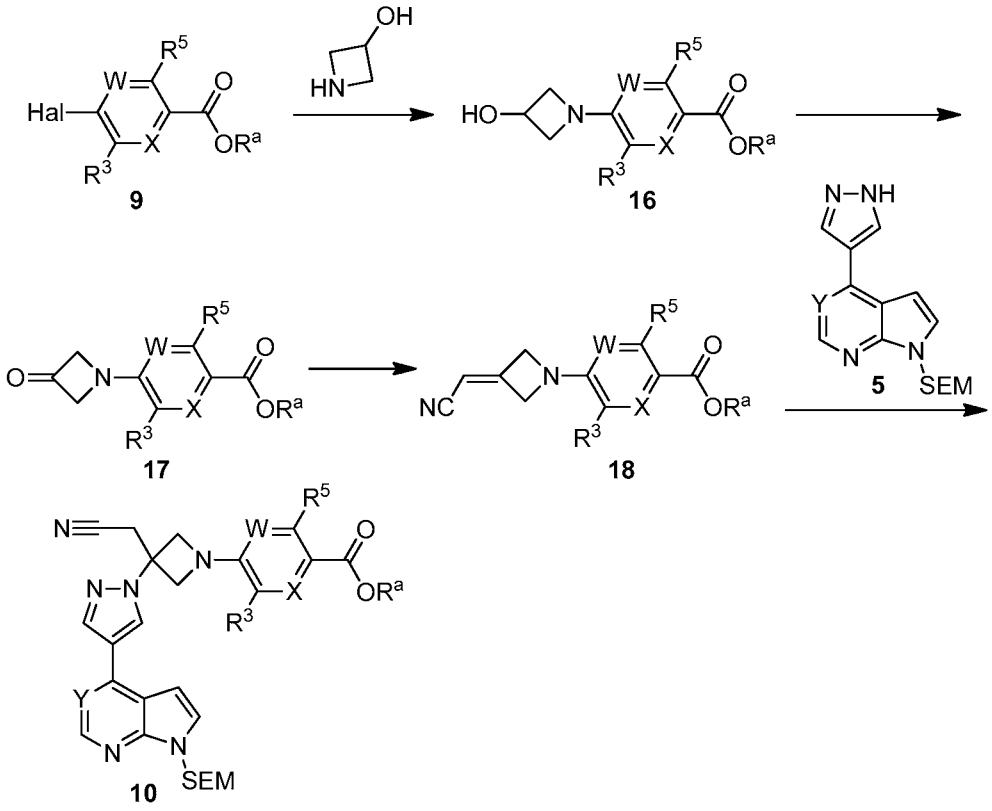
Scheme 2



A series of aryl ester derivatives **10** can be prepared according to the methods outlined in Scheme 3. Replacement of the leaving group Hal (Hal can be halogen, OTs or OTf) in **9** by 3-hydroazetidine to produce compound **16** can be achieved under thermal conditions in a suitable solvent such as, but not limited to, DMSO, dioxane, DMF, or NMP in the presence of a base such as potassium carbonate, cesium carbonate, or sodium carbonate; or under copper-catalyzed Ullmann type N-arylation reaction conditions by using copper(I) iodide and potassium carbonate; or under palladium-catalyzed C-N bond forming reaction conditions using Xantphos [4,5-bis(diphenylphosphino)-9,9-dimetnylxanthene], BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl], or P(o-Tol)3 [tri(o-tolyl)phosphine] as the ligand and potassium carbonate or cesium carbonate or potassium tert-butoxide as the base. α,β-

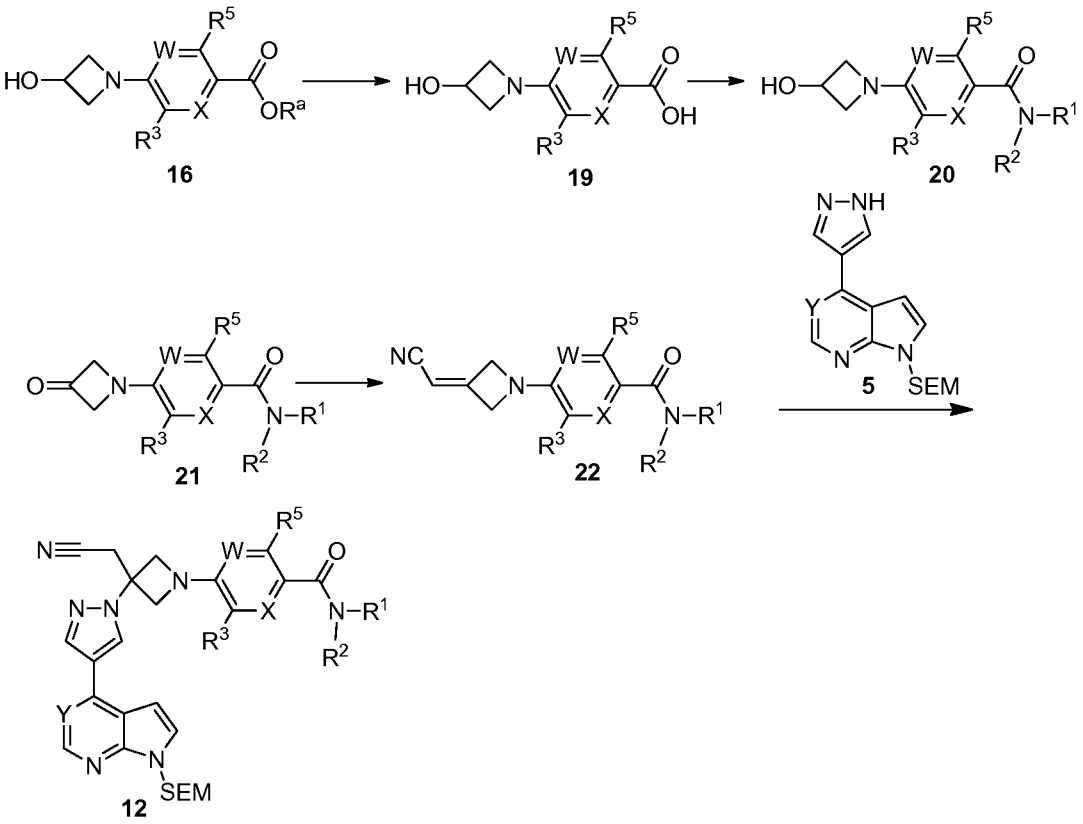
Unsaturated nitrile **18** can be obtained by Wittig's reaction of diethyl cyanomethylphosphonate with the ketone **17** which can be given by Swern oxidation of **16**. Michael addition of **5** with α,β-unsaturated nitrile **18** can afford the adduct **10**.

Scheme 3



Similarly, a series of aryl amide derivatives **12** can be prepared according to the procedures outlined in Scheme 4. The aryl ester **16** can be hydrolyzed to the corresponding acid **19** by using an alkali such as lithium hydroxide, sodium hydroxide or potassium hydroxide. The acid **19** can be transfered to the arylamide **20** by reaction with an appropriate amine in the presence of a suitable coupling reagent such as, but not limited to, BOP, PyOP, HATU, HBTU, EDC, or CDI. Swern oxidation of **20** can produce the corresponding ketone **21** which can be converted to the α,β-unsaturated nitrile **22** by Wittig's reaction with diethyl cyanomethylphosphonate. Michael addition of **5** with α,β-unsaturated nitrile **21** can afford the adduct **12**.

Scheme 4


HO
N
W
X
R5
R3
O
ORa
16
OH
19
N–R1
R2
20
N–NH
Y
N
SEM
5
O
21
NC
22
12

Methods

Compounds of the invention are JAK inhibitors, and the majority of the compounds of the invention, are JAK1 selective inhibitors. A JAK1 selective inhibitor is a compound that inhibits JAK1 activity preferentially over other Janus kinases. For example, the compounds of the invention preferentially inhibit JAK1 over one or more of JAK2, JAK3, and TYK2. In some embodiments, the compounds inhibit JAK1 preferentially over JAK2 (e.g., have a JAK1/JAK2 IC_{50} ratio >1) as calculated by measuring IC_{50} at 1 mM ATP (e.g., see Example A). In some embodiments, the compounds are greater than about 10-fold more selective for JAK1 over JAK2, as calculated by measuring IC_{50} at 1 mM ATP. In some embodiments, the compounds are greater than about 15-fold selective for JAK1 over JAK2, as calculated by measuring IC_{50} at 1 mM ATP. In some embodiments, the compounds are greater than about 20-fold selective for JAK1 over JAK2, as calculated by measuring IC_{50} at 1 mM ATP.

JAK1 plays a central role in a number of cytokine and growth factor signaling pathways that, when dysregulated, can result in or contribute to disease states. For example, IL-6 levels are elevated in rheumatoid arthritis, a disease in which it has been suggested to have detrimental effects (Fonesca, J.E. et al., Autoimmunity Reviews, 8:538-42, 2009). Because IL-6 signals, at least in part, through JAK1, antagonizing IL-6 directly or indirectly through JAK1 inhibition is expected to provide clinical benefit (Guschin, D., N., et al Embo J 14:1421, 1995; Smolen, J. S., et al. Lancet 371:987, 2008). Moreover, in some cancers JAK1 is mutated resulting in constitutive undesirable tumor cell growth and survival (Mullighan CG, Proc Natl Acad Sci U S A.106:9414-8, 2009; Flex E., et al.J Exp Med. 205:751-8, 2008). In other autoimmune diseases and cancers elevated systemic levels of inflammatory cytokines that activate JAK1 may also contribute to the disease and/or associated symptoms. Therefore, patients with such diseases may benefit from JAK1 inhibition. Selective inhibitors of JAK1 may be efficacious while avoiding unnecessary and potentially undesirable effects of inhibiting other JAK kinases.

Selective inhibitors of JAK1, relative to other JAK kinases, may have multiple therapeutic advantages over less selective inhibitors. With respect to selectivity against JAK2, a number of important cytokines and growth factors signal through JAK2 including, for example, erythropoietin (Epo) and thrombopoietin (Tpo)

(Parganas E, et al. Cell. 93:385-95, 1998). Epo is a key growth factor for red blood cells production; hence a paucity of Epo-dependent signaling can result in reduced numbers of red blood cells and anemia (Kaushansky K, NEJM 354:2034-45, 2006). Tpo, another example of a JAK2-dependent growth factor, plays a central role in controlling the proliferation and maturation of megakaryocytes – the cells from which platelets are produced (Kaushansky K, NEJM 354:2034-45, 2006). As such, reduced Tpo signaling would decrease megakaryocyte numbers (megakaryocytopenia) and lower circulating platelet counts (thrombocytopenia). This can result in undesirable and/or uncontrollable bleeding. Reduced inhibition of other JAKs, such as JAK3 and Tyk2, may also be desirable as humans lacking functional version of these kinases have been shown to suffer from numerous maladies such as severe-combined immunodeficiency or hyperimmunoglobulin E syndrome (Minegishi, Y, et al. Immunity 25:745-55, 2006; Macchi P, et al. Nature. 377:65-8, 1995). Therefore a JAK1 inhibitor with reduced affinity for other JAKs would have significant advantages over a less-selective inhibitor with respect to reduced side effects involving immune suppression, anemia and thrombocytopenia.

Another aspect of the present invention pertains to methods of treating a JAK-associated disease or disorder in an individual (*e.g.*, patient) by administering to the individual in need of such treatment a therapeutically effective amount or dose of a compound of the present invention or a pharmaceutical composition thereof. A JAK-associated disease can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of the JAK, including overexpression and/or abnormal activity levels. A JAK-associated disease can also include any disease, disorder or condition that can be prevented, ameliorated, or cured by modulating JAK activity.

Examples of JAK-associated diseases include diseases involving the immune system including, for example, organ transplant rejection (*e.g.*, allograft rejection and graft versus host disease).

Further examples of JAK-associated diseases include autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, psoriasis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, myasthenia gravis, immunoglobulin nephropathies, myocarditis, autoimmune thyroid disorders, chronic obstructive pulmonary disease (COPD), and

the like. In some embodiments, the autoimmune disease is an autoimmune bullous skin disorder such as pemphigus vulgaris (PV) or bullous pemphigoid (BP).

Further examples of JAK-associated diseases include allergic conditions such as asthma, food allergies, eszematous dermatitis, contact dermatitis, atopic dermatitis (atropic eczema), and rhinitis. Further examples of JAK-associated diseases include viral diseases such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV) and Human Papilloma Virus (HPV).

Further examples of JAK-associated disease include diseases associated with cartilage turnover, for example, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflex sympathetic dystrophy, algodystrophy, Tietze syndrome, costal athropathy, osteoarthritis deformans endemica, Mseleni disease, Handigodu disease, degeneration resulting from fibromyalgia, systemic lupus erythematosus, scleroderma, or ankylosing spondylitis.

Further examples of JAK-associated disease include congenital cartilage malformations, including hereditary chrondrolysis, chrondrodysplasias, and pseudochrondrodysplasias (e.g., microtia, enotia, and metaphyseal chrondrodysplasia).

Further examples of JAK-associated diseases or conditions include skin disorders such as psoriasis (for example, psoriasis vulgaris), atopic dermatitis, skin rash, skin irritation, skin sensitization (*e.g.*, contact dermatitis or allergic contact dermatitis). For example, certain substances including some pharmaceuticals when topically applied can cause skin sensitization. In some embodiments, co-administration or sequential administration of at least one JAK inhibitor of the invention together with the agent causing unwanted sensitization can be helpful in treating such unwanted sensitization or dermatitis. In some embodiments, the skin disorder is treated by topical administration of at least one JAK inhibitor of the invention.

In further embodiments, the JAK-associated disease is cancer including those characterized by solid tumors (*e.g.*, prostate cancer, renal cancer, hepatic cancer, pancreatic cancer, gastric cancer, breast cancer, lung cancer, cancers of the head and neck, thyroid cancer, glioblastoma, Kaposi's sarcoma, Castleman's disease, uterine leiomyosarcoma, melanoma etc.), hematological cancers (*e.g.*, lymphoma, leukemia such as acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) or multiple myeloma), and skin cancer such as cutaneous T-cell lymphoma (CTCL) and

cutaneous B-cell lymphoma. Example CTCLs include Sezary syndrome and mycosis fungoides.

In some embodiments, the JAK inhibitors described herein, or in combination with other JAK inhibitors, such as those reported in U.S. Ser. No. 11/637,545, which is incorporated herein by reference in its entirety, can be used to treat inflammation-associated cancers. In some embodiments, the cancer is associated with inflammatory bowel disease. In some embodiments, the inflammatory bowel disease is ulcerative colitis. In some embodiments, the inflammatory bowel disease is Crohn's disease. In some embodiments, the inflammation-associated cancer is colitis-associated cancer. In some embodiments, the inflammation-associated cancer is colon cancer or colorectal cancer. In some embodiments, the cancer is gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), adenocarcinoma, small intestine cancer, or rectal cancer.

JAK-associated diseases can further include those characterized by expression of: JAK2 mutants such as those having at least one mutation in the pseudo-kinase domain (*e.g.*, JAK2V617F); JAK2 mutants having at least one mutation outside of the pseudo-kinase domain; JAK1 mutants; JAK3 mutants; erythropoietin receptor (EPOR) mutants; or deregulated expression of CRLF2.

JAK-associated diseases can further include myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD), and the like. In some embodiments, the myeloproliferative disorder is myelofibrosis (e.g., primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (Post-PV MF) or post-essential thrombocythemia myelofibrosis (Post-ET MF)). In some embodiments, the myeloproliferative disorder is myelofibrosis with myeloid metaplasia (MMM). In some embodiments, the myeloproliferative disorder is post-essential thrombocythemia myelofibrosis (Post-ET MF). In some embodiments, the myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF).

The present invention further provides methods of treating psoriasis or other skin disorders by administration of a topical formulation containing a compound of the invention.

In some embodiments, JAK inhibitors described herein can be used to treat pulmonary arterial hypertension.

The present invention further provides a method of treating dermatological side effects of other pharmaceuticals by administration of the compound of the invention. For example, numerous pharmaceutical agents result in unwanted allergic reactions which can manifest as acneiform rash or related dermatitis. Example pharmaceutical agents that have such undesirable side effects include anti-cancer drugs such as gefitinib, cetuximab, erlotinib, and the like. The compounds of the invention can be administered systemically or topically (e.g., localized to the vicinity of the dermatitis) in combination with (e.g., simultaneously or sequentially) the pharmaceutical agent having the undesirable dermatological side effect. In some embodiments, the compound of the invention can be administered topically together with one or more other pharmaceuticals, where the other pharmaceuticals when topically applied in the absence of a compound of the invention cause contact dermatitis, allergic contact sensitization, or similar skin disorder. Accordingly, compositions of the invention include topical formulations containing the compound of the invention and a further pharmaceutical agent which can cause dermatitis, skin disorders, or related side effects.

Further JAK-associated diseases include inflammation and inflammatory diseases. Example inflammatory diseases include sarcoidosis, inflammatory diseases of the eye (*e.g.*, iritis, uveitis, scleritis, conjunctivitis, or related disease), inflammatory diseases of the respiratory tract (*e.g.*, the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lower respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis, and other inflammatory diseases. In some embodiments, the inflammation disease of the eye is blepharitis.

The JAK inhibitors described herein can further be used to treat ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest. The JAK inhibitors described herein can further be used to treat endotoxin-driven disease state (e.g., complications after bypass surgery or chronic endotoxin states contributing to chronic cardiac failure). The JAK inhibitors described herein can further be used to treat anorexia, cachexia, or fatigue such as that resulting from or associated with cancer. The JAK inhibitors described herein can further be used to treat restenosis, sclerodermitis, or fibrosis. The JAK

inhibitors described herein can further be used to treat conditions associated with hypoxia or astrogliosis such as, for example, diabetic retinopathy, cancer, or neurodegeneration. See, e.g., Dudley, A.C. *et al. Biochem. J.* 2005, 390(Pt 2):427-36 and Sriram, K. *et al. J. Biol. Chem*. 2004, 279(19):19936-47. Epub 2004 Mar 2, both of which are incorporated herein by reference in their entirety. The JAK inhibitors described herein can be used to treat Alzheimer's disease.

The JAK inhibitors described herein can further be used to treat other inflammatory diseases such as systemic inflammatory response syndrome (SIRS) and septic shock.

The JAK inhibitors described herein can further be used to treat gout and increased prostate size due to, e.g., benign prostatic hypertrophy or benign prostatic hyperplasia.

Further JAK-associated diseases include bone resorption diseases such as osteoporosis, osteoarthritis. Bone resorption can also be associated with other conditions such as hormonal imbalance and/or hormonal therapy, autoimmune disease (e.g. osseous sarcoidosis), or cancer (e.g. myeloma). The reduction of the bone resorption due to the JAK inhibitors can be about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

In some embodiments, JAK inhibitors described herein can further be used to treat a dry eye disorder. As used herein, "dry eye disorder" is intended to encompass the disease states summarized in a recent official report of the Dry Eye Workshop (DEWS), which defined dry eye as "a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface." Lemp, "The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye Workshop", *The Ocular Surface*, 5(2), 75-92 April 2007, which is incorporated herein by reference in its entirety. In some embodiments, the dry eye disorder is selected from aqueous tear-deficient dry eye (ADDE) or evaporative dry eye disorder, or appropriate combinations thereof. In some embodiments, the dry eye disorder is Sjogren syndrome dry eye (SSDE). In some embodiments, the dry eye disorder is non-Sjogren syndrome dry eye (NSSDE).

In a further aspect, the present invention provides a method of treating conjunctivitis, uveitis (including chronic uveitis), chorioditis, retinitis, cyclitis, sclieritis, episcleritis, or iritis; treating inflammation or pain related to corneal transplant, LASIK (laser assisted in situ keratomileusis), photorefractive keratectomy, or LASEK (laser assisted sub-epithelial keratomileusis); inhibiting loss of visual acuity related to corneal transplant, LASIK, photorefractive keratectomy, or LASEK; or inhibiting transplant rejection in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of the compound of the invention, or a pharmaceutically acceptable salt thereof.

Additionally, the compounds of the invention, or in combination with other JAK inhibitors, such as those reported in U.S. Ser. No. 11/637,545, which is incorporated herein by reference in its entirety, can be used to treat respiratory dysfunction or failure associated wth viral infection, such as influenza and SARS.

In some embodiments, the present invention provides a compound as described in any of the embodiments herein, or a pharmaceutically acceptable salt thereof, for use in a method of treating any of the diseases or disorders described herein. In some embodiments, the present invention provides the use of a compound as described in any of the embodiments herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in a method of treating any of the diseases or disorders described herein.

In some embodiments, the present invention provides a compound as described in any of the embodiments herein, or a pharmaceutically acceptable salt thereof, for use in a method of modulating JAK1. In some embodiments, the present invention also provides use of a compound as described in any of the embodiments herein, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in a method of modulating JAK1.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" a JAK with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having a JAK, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the JAK.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician. In some embodiments, the therapeutically effective amount is about 5 mg to about 1000 mg, or about 10 mg to about 500 mg.

As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease. In one embodiment, treating or treatment includes preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease.

Combination Therapies

One or more additional pharmaceutical agents such as, for example, chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors such as, for example, those described in WO 2006/056399, which is incorporated herein by reference in its entirety, or other agents can be used in combination with the compounds described herein for treatment of JAK-associated diseases, disorders or conditions. The one or more additional pharmaceutical agents can be administered to a patient simultaneously or sequentially.

Example chemotherapeutics include proteosome inhibitors (*e.g.*, bortezomib), thalidomide, revlimid, and DNA-damaging agents such as melphalan, doxorubicin, cyclophosphamide, vincristine, etoposide, carmustine, and the like.

Example steroids include coriticosteroids such as dexamethasone or prednisone.

Example Bcr-Abl inhibitors include the compounds, and pharmaceutically acceptable salts thereof, of the genera and species disclosed in U.S. Pat. No. 5,521,184, WO 04/005281, and U.S. Ser. No. 60/578,491, all of which are incorporated herein by reference in their entirety.

Example suitable Flt-3 inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 03/037347, WO 03/099771, and WO 04/046120, all of which are incorporated herein by reference in their entirety.

Example suitable RAF inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 00/09495 and WO 05/028444, both of which are incorporated herein by reference in their entirety.

Example suitable FAK inhibitors include compounds, and their pharmaceutically acceptable salts, as disclosed in WO 04/080980, WO 04/056786, WO 03/024967, WO 01/064655, WO 00/053595, and WO 01/014402, all of which are incorporated herein by reference in their entirety.

In some embodiments, one or more of the compounds of the invention can be used in combination with one or more other kinase inhibitors including imatinib, particularly for treating patients resistant to imatinib or other kinase inhibitors.

In some embodiments, one or more JAK inhibitors of the invention can be used in combination with a chemotherapeutic in the treatment of cancer, such as multiple myeloma, and may improve the treatment response as compared to the response to the chemotherapeutic agent alone, without exacerbation of its toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma, for example, can include, without limitation, melphalan, melphalan plus prednisone [MP], doxorubicin, dexamethasone, and Velcade (bortezomib). Further additional agents used in the treatment of multiple myeloma include Bcr-Abl, Flt-3, RAF and FAK kinase inhibitors. Additive or synergistic effects are desirable outcomes of combining a JAK inhibitor of the present invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone may be reversible upon treatment with a JAK inhibitor of the present invention. The agents can be combined with the present compounds in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with at least one JAK inhibitor where the dexamethasone is administered intermittently as opposed to continuously.

In some further embodiments, combinations of one or more JAK inhibitors of the invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplant or stem cell transplant.

In some embodiments, the additional therapeutic agent is fluocinolone acetonide (Retisert®), or rimexolone (AL-2178, Vexol, Alcon).

In some embodiments, the additional therapeutic agent is cyclosporine (Restasis®).

In some embodiments, the additional therapeutic agent is a corticosteroid. In some embodiments, the corticosteroid is triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, or flumetholone.

In some embodiments, the additional therapeutic agent is selected from Dehydrex™ (Holles Labs), Civamide (Opko), sodium hyaluronate (Vismed, Lantibio/TRB Chemedia), cyclosporine (ST-603, Sirion Therapeutics), ARG101(T) (testosterone, Argentis), AGR1012(P) (Argentis), ecabet sodium (Senju-Ista), gefarnate (Santen), 15-(s)-hydroxyeicosatetraenoic acid (15(S)-HETE), cevilemine, doxycycline (ALTY-0501, Alacrity), minocycline, iDestrin™ (NP50301, Nascent Pharmaceuticals), cyclosporine A (Nova22007, Novagali), oxytetracycline (Duramycin, MOLI1901, Lantibio), CF101 (2S,3S,4R,5R)-3,4-dihydroxy-5-[6-[(3-iodophenyl)methylamino]purin-9-yl]-N-methyl-oxolane-2-carbamyl, Can-Fite Biopharma), voclosporin (LX212 or LX214, Lux Biosciences), ARG103 (Agentis), RX-10045 (synthetic resolvin analog, Resolvyx), DYN15 (Dyanmis Therapeutics), rivoglitazone (DE011, Daiichi Sanko), TB4 (RegeneRx), OPH-01 (Ophtalmis Monaco), PCS101 (Pericor Science), REV1-31 (Evolutec), Lacritin (Senju), rebamipide (Otsuka-Novartis), OT-551 (Othera), PAI-2 (University of Pennsylvania and Temple University), pilocarpine, tacrolimus, pimecrolimus (AMS981, Novartis), loteprednol etabonate, rituximab, diquafosol tetrasodium (INS365, Inspire), KLS-0611 (Kissei Pharmaceuticals), dehydroepiandrosterone, anakinra, efalizumab, mycophenolate sodium, etanercept (Embrel®), hydroxychloroquine, NGX267 (TorreyPines Therapeutics), actemra, gemcitabine, oxaliplatin, L-asparaginase, or thalidomide.

In some embodiments, the additional therapeutic agent is an anti-angiogenic agent, cholinergic agonist, TRP-1 receptor modulator, a calcium channel blocker, a mucin secretagogue, MUC1 stimulant, a calcineurin inhibitor, a corticosteroid, a P2Y2 receptor agonist, a muscarinic receptor agonist, an mTOR inhibitor, another JAK inhibitor, Bcr-Abl kinase inhibitor, Flt-3 kinase inhibitor, RAF kinase inhibitor, and FAK kinase inhibitor such as, for example, those described in WO 2006/056399, which is incorporated herein by reference in its entirety. In some embodiments, the additional therapeutic agent is a tetracycline derivative (e.g., minocycline or doxycline). In some embodiments, the additional therapeutic agent binds to FKBP12.

In some embodiments, the additional therapeutic agent is an alkylating agent or DNA cross-linking agent; an anti-metabolite/demethylating agent (e.g., 5-flurouracil, capecitabine or azacitidine); an anti-hormone therapy (e.g., hormone receptor antagonists, SERMs, or aromotase inhibitor); a mitotic inhibitor (e.g. vincristine or paclitaxel); an topoisomerase (I or II) inhibitor (e.g. mitoxantrone and irinotecan); an apoptotic inducers (e.g. ABT-737); a nucleic acid therapy (e.g. antisense or RNAi); nuclear receptor ligands (e.g., agonists and/or antagonists: all-trans retinoic acid or bexarotene); epigenetic targeting agents such as histone deacetylase inhibitors (e.g. vorinostat), hypomethylating agents (e.g. decitabine); regulators of protein stability such as Hsp90 inhibitors, ubiquitin and/or ubiquitin like conjugating or deconjugating molecules; or an EGFR inhibitor (erlotinib).

In some embodiments, the additional therapeutic agent(s) are demulcent eye drops (also known as “artificial tears”), which include, but are not limited to, compositions containing polyvinylalcohol, hydroxypropyl methylcellulose, glycerin, polyethylene glycol (e.g. PEG400), or carboxymethyl cellulose. Artificial tears can help in the treatment of dry eye by compensating for reduced moistening and lubricating capacity of the tear film. In some embodiments, the additional therapeutic agent is a mucolytic drug, such as N-acetyl-cysteine, which can interact with the mucoproteins and, therefore, to decrease the viscosity of the tear film.

In some embodiments, the additional therapeutic agent includes an antibiotic, antiviral, antifungal, anesthetic, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin;

naphthyridine; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; cromolyn; lodoxamide; levocabastin; naphazoline; antazoline; pheniramine; or azalide antibiotic.

In some embodiments, the additional therapeutic agent is an inhibitor of one or more Pim kinases. The second therapeutic agent in the methods and compositions of the present invention can be any active agent, such as a chemical compound or a macromolecule or a biopolymer, that inhibits at least one Pim kinase, such as Pim-1, Pim-2, or Pim-3. In some embodiments, the Pim inhibitor inhibits Pim-1. In some embodiments, the Pim inhibitor inhibits Pim-2. In some embodiments, the Pim inhibitor inhibits Pim-3. In some embodiments, the Pim inhibitor inhibits Pim-1, Pim-2, and Pim-3. In some embodiments, the Pim inhibitor is selective for one or more Pims over other kinases. In further embodiments, the Pim inhibitor is a selective inhibitor of Pim-1 over Pim-2 and Pim-3. In further embodiments, the Pim inhibitor is a selective inhibitor of Pim-2 over Pim-1 and Pim-3. In yet further embodiments, the Pim inhibitor is a selective inhibitor of Pim-3 over Pim-1 and Pim-2.

A selective Pim inhibitor generally inhibits the Pim kinase target it is selective for with more potency than for the target is it selective against. In some embodiments, the selectivity can be at least about 2-fold, at least about 3-fold, at least about 5-fold, at least about 10-fold, at least about 20-fold, at least about 50-fold, or at least about 100-fold. Potency can be measured by one or more in vitro assays, such as the assays provided below in the Examples.

Example Pim kinase inhibitors include the compounds described in U.S. Pat. No. 7,750,007, WO 2011/057784, WO 2011/029802, WO 2010/026121, WO 2010/026122, WO 2010/026124, WO 2010/022081, WO 2010/022076, WO 2010/001169, WO 2010/000978, WO 2009/064486, WO 2009/109576, WO 2008/106692, WO 2008/124323 (US 2010/029633), WO 2008/082840 (US 2008/161578), WO 2008/082839 (U.S. Pat. App. Pub. No. 2008/161559), WO 2008/058126 (U.S. Pat. No. 7,750,007), and WO 2008/022164 (U.S. Pat. App. Pub. No. 2010/210627), each of which is incorporated herein by reference in its entirety.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, the compounds of the invention can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (*e.g.*, by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, *e.g.*, intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, the compound of the invention or a pharmaceutically acceptable salt thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions of the invention, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be

adjusted by milling to provide a substantially uniform distribution in the formulation, *e.g.* about 40 mesh.

The compounds of the invention may be milled using known milling procedures such as wet milling to obtain a particle size appropriate for tablet formation and for other formulation types. Finely divided (nanoparticulate) preparations of the compounds of the invention can be prepared by processes known in the art, e.g., see International App. No. WO 2002/000196.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

In some embodiments, the pharmaceutical composition comprises silicified microcrystalline cellulose (SMCC) and at least one compound described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the silicified microcrystalline cellulose comprises about 98% microcrystalline cellulose and about 2% silicon dioxide w/w.

In some embodiments, the composition is a sustained release composition comprising at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and at least one component selected from microcrystalline cellulose, lactose monohydrate, hydroxypropyl methylcellulose, and polyethylene oxide. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate, and hydroxypropyl methylcellulose. In some embodiments, the composition comprises at least one compound described herein, or a pharmaceutically acceptable salt thereof, and microcrystalline cellulose, lactose monohydrate, and polyethylene oxide. In some embodiments, the

composition further comprises magnesium stearate or silicon dioxide. In some embodiments, the microcrystalline cellulose is Avicel PH102™. In some embodiments, the lactose monohydrate is Fast-flo 316™. In some embodiments, the hydroxypropyl methylcellulose is hydroxypropyl methylcellulose 2208 K4M (e.g., Methocel K4 M Premier™) and/or hydroxypropyl methylcellulose 2208 K100LV (e.g., Methocel K00LV™). In some embodiments, the polyethylene oxide is polyethylene oxide WSR 1105 (e.g., Polyox WSR 1105™).

In some embodiments, a wet granulation process is used to produce the composition. In some embodiments, a dry granulation process is used to produce the composition.

The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. In some embodiments, each dosage contains about 10 mg of the active ingredient. In some embodiments, each dosage contains about 50 mg of the active ingredient. In some embodiments, each dosage contains about 25 mg of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

In some embodiments, the compositions of the invention contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

In some embodiments, the compositions of the invention contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient.

In some embodiments, the compositions of the invention contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the

art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, about 0.1 to about 1000 mg of the active ingredient of the present invention.

The tablets or pills of the present invention can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the compounds and compositions of the present invention can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored

emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

Topical formulations can contain one or more conventional carriers. In some embodiments, ointments can contain water and one or more hydrophobic carriers selected from, for example, liquid paraffin, polyoxyethylene alkyl ether, propylene glycol, white Vaseline, and the like. Carrier compositions of creams can be based on water in combination with glycerol and one or more other components, e.g. glycerinemonostearate, PEG-glycerinemonostearate and cetylstearyl alcohol. Gels can be formulated using isopropyl alcohol and water, suitably in combination with other components such as, for example, glycerol, hydroxyethyl cellulose, and the like. In some embodiments, topical formulations contain at least about 0.1, at least about 0.25, at least about 0.5, at least about 1, at least about 2, or at least about 5 wt % of the compound of the invention. The topical formulations can be suitably packaged in tubes of, for example, 100 g which are optionally associated with instructions for the treatment of the select indication, e.g., psoriasis or other skin condition.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of a compound of the present invention can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound of the invention in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds of the invention can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The compositions of the invention can further include one or more additional pharmaceutical agents such as a chemotherapeutic, steroid, anti-inflammatory compound, or immunosuppressant, examples of which are listed hereinabove.
In some embodiments, the compound, or pharmaceutically acceptable salt thereof, is administered as an ophthalmic composition. Accordingly, in some embodiments, the methods comprise administration of the compound, or pharmaceutically acceptable salt thereof, and an ophthalmically acceptable carrier. In some embodiments, the

ophthalmic composition is a liquid composition, semi-solid composition, insert, film, microparticles or nanoparticles.

In some embodiments, the ophthalmic composition is a liquid composition. In some embodiments, the ophthalmic composition is a semi-solid composition. In some embodiments, the ophthalmic composition is a topical composition. The topical compositions include, but are not limited to liquid and semi-solid compositions. In some embodiments, the ophthalmic composition is a topical composition. In some embodiments, the topical composition comprises aqueous solution, an aqueous suspension, an ointment or a gel. In some embodiments, the ophthalmic composition is topically applied to the front of the eye, under the upper eyelid, on the lower eyelid and in the cul-de-sac. In some embodiments, the ophthalmic composition is sterilized. The sterilization can be accomplished by known techniques like sterilizing filtration of the solution or by heating of the solution in the ampoule ready for use. The ophthalmic compositions of the invention can further contain pharmaceutical excipients suitable for the preparation of ophthalmic formulations. Examples of such excipients are preserving agents, buffering agents, chelating agents, antioxidant agents and salts for regulating the osmotic pressure.

As used herein, the term "ophthalmically acceptable carrier" refers to any material that can contain and release the compound, or pharmaceutically acceptable salt thereof, and that is compatible with the eye. In some embodiments, the ophthalmically acceptable carrier is water or an aqueous solution or suspension, but also includes oils such as those used to make ointments and polymer matrices such as used in ocular inserts. In some embodiments, the composition may be an aqueous suspension comprising the compound, or pharmaceutically acceptable salt thereof. Liquid ophthalmic compositions, including both ointments and suspensions, may have a viscosity that is suited for the selected route of administration. In some embodiments, the ophthalmic composition has a viscosity in the range of from about 1,000 to about 30,000 centipoise.

In some embodiments, the ophthalmic compositions may further comprise one or more of surfactants, adjuvants, buffers, antioxidants, tonicity adjusters, preservatives (e.g., EDTA, BAK (benzalkonium chloride), sodium chlorite, sodium perborate, polyquaterium-1), thickeners or viscosity modifiers (e.g., carboxymethyl cellulose, hydroxymethyl cellulose, polyvinyl alcohol, polyethylene glycol, glycol 400, propylene glycol hydroxymethyl cellulose, hydroxpropyl-guar, hyaluronic acid,

and hydroxypropyl cellulose) and the like. Additives in the formulation may include, but are not limited to, sodium chloride, sodium bicarbonate, sorbic acid, methyl paraben, propyl paraben, chlorhexidine, castor oil, and sodium perborate.

Aqueous ophthalmic compositions (solutions or suspensions) generally do not contain physiologically or ophthalmically harmful constituents. In some embodiments, purified or deionized water is used in the composition. The pH may be adjusted by adding any physiologically and ophthalmically acceptable pH adjusting acids, bases or buffers to within the range of about 5.0 to 8.5. Ophthalmically acceptable examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, trishydroxymethylamino-methane, and the like. Salts and buffers include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

In some embodiments, the methods involve forming or supplying a depot of the therapeutic agent in contact with the external surface of the eye. A depot refers to a source of therapeutic agent that is not rapidly removed by tears or other eye clearance mechanisms. This allows for continued, sustained high concentrations of therapeutic agent to be present in the fluid on the external surface of the eye by a single application. Without wishing to be bound by any theory, it is believed that absorption and penetration may be dependent on both the dissolved drug concentration and the contact duration of the external tissue with the drug containing fluid. As the drug is removed by clearance of the ocular fluid and/or absorption into the eye tissue, more drug is provided, e.g. dissolved, into the replenished ocular fluid from the depot. Accordingly, the use of a depot may more easily facilitate loading of the ocular tissue for more insoluble therapeutic agents. In some embodiments, the depot can remain for up to eight hours or more. In some embodiments, the ophthalmic depot forms includes, but is not limited to, aqueous polymeric suspensions, ointments, and solid inserts.

In some embodiments, the ophthalmic composition is an ointment or gel. In some embodiment, the ophthalmic composition is an oil-based delivery vehicle. In some embodiments, the composition comprises a petroleum or lanolin base to which is added the active ingredient, usually as 0.1 to 2%, and excipients. Common bases

may include, but are not limited to, mineral oil, petrolatum and combinations thereof. In some embodiments, the ointment is applied as a ribbon onto the lower eyelid.

In some embodiments, the ophthalmic composition is an ophthalmic insert. In some embodiments, the ophthalmic insert is biologically inert, soft, bio-erodible, viscoelastic, stable to sterilization after exposure to therapeutic agents, resistant to infections from air borne bacteria, bio- erodible, biocompatible, and/or viscoelastic. In some embodiments, the insert comprises an ophthalmically acceptable matrix, e.g., a polymer matrix. The matrix is typically a polymer and the therapeutic agent is generally dispersed therein or bonded to the polymer matrix. In some embodiments, the therapeutic agent may be slowly released from the matrix through dissolution or hydrolysis of the covalent bond. In some embodiments, the polymer is bioerodible (soluble) and the dissolution rate thereof can control the release rate of the therapeutic agent dispersed therein. In another form, the polymer matrix is a biodegradable polymer that breaks down such as by hydrolysis to thereby release the therapeutic agent bonded thereto or dispersed therein. In further embodiments, the matrix and therapeutic agent can be surrounded with an additional polymeric coating to further control release. In some embodiments, the insert comprises a biodegradable polymer such as polycaprolactone (PCL), an ethylene/vinyl acetate copolymer (EVA), polyalkyl cyanoacrylate, polyurethane, a nylon, or poly (dl-lactide-co-glycolide) (PLGA), or a copolymer of any of these. In some embodiments, the therapeutic agent is dispersed into the matrix material or dispersed amongst the monomer composition used to make the matrix material prior to polymerization. In some embodiments, the amount of therapeutic agent is from about 0.1 to about 50%, or from about 2 to about 20%. In further embodiments, the biodegradable or bioerodible polymer matrix is used so that the spent insert does not have to be removed. As the biodegradable or bioerodible polymer is degraded or dissolved, the therapeutic agent is released.

In further embodiments, the ophthalmic insert comprises a polymer, including, but are not limited to, those described in Wagh, et al., "Polymers used in ocular dosage form and drug delivery systems", *Asian J. Pharm.,* pages 12-17 (Jan. 2008), which is incorporated herein by reference in its entirety. In some embodiments, the insert comprises a polymer selected from polyvinylpyrrolidone (PVP), an acrylate or methacrylate polymer or copolymer (e.g., Eudragit® family of polymers from Rohm or Degussa), hydroxymethyl cellulose, polyacrylic acid, poly(amidoamine) dendrimers, poly(dimethyl siloxane), polyethylene oxide, poly(lactide-co-glycolide),

poly(2-hydroxyethylmethacrylate), poly(vinyl alcohol), or poly(propylene fumarate). In some embodiments, the insert comprises Gelfoam® R. In some embodiments, the insert is a polyacrylic acid of 450 kDa-cysteine conjugate.

In some embodiments, the ophthalmic composition is a ophthalmic film. Polymers suitable for such films include, but are not limited to, those described in Wagh, et al. (*ibid*), In some embodiments, the film is a soft-contact lens, such as ones made from copolymers of N,N-diethylacrylamide and methacrylic acid crosslinked with ethyleneglycol dimethacrylate.

In some embodiments, the ophthalmic compositon comprises microspheres or nanoparticles. In some embodiment, the microspheres comprise gelatin. In some embodiments, the microspheres are injected to the posterior segment of the eye, in the chroroidal space, in the sclera, intravitreally or sub-retinally. In some embodiments, the microspheres or nanoparticles comprises a polymer including, but not limited to, those described in Wagh, et al. (*ibid*), which is incorporated herein by reference in its entirety. In some embodiments, the polymer is chitosan, a polycarboxylic acid such as polyacrylic acid, albumin particles, hyaluronic acid esters, polyitaconic acid, poly(butyl)cyanoacrylate, polycaprolactone, poly(isobutyl)caprolactone, poly(lactic acid-co-glycolic acid), or poly(lactic acid). In some embodiments, the microspheres or nanoparticles comprise solid lipid particles.

In some embodiments, the ophthalmic composition comprises an ion-exchange resin. In some embodiments, the ion-exchange resin is an inorganic zeolite or synthetic organic resin. In some embodiments, the ion-exchange resin includes, but is not limited to, those described in Wagh, et al. (*ibid*), which is incorporated herein by reference in its entirety. In some embodiments, the ion-exhange resin is a partially neutralized polyacrylic acid.

In some embodiments, the ophthalmic composition is an aqueous polymeric suspension. In some embodiments, the therapeutic agent or a polymeric suspending agent is suspended in an aqueous medium. In some embodiments, the aqueous polymeric suspensions may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. In some embodiments, they may be formulated so that there is increased gelation upon contact with tear fluid.

Labeled Compounds and Assay Methods

Another aspect of the present invention relates to labeled compounds of the invention (radio-labeled, fluorescent-labeled, etc.) that would be useful not only in imaging techniques but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating JAK in tissue samples, including human, and for identifying JAK ligands by inhibition binding of a labeled compound. Accordingly, the present invention includes JAK assays that contain such labeled compounds.

The present invention further includes isotopically-labeled compounds of the invention. An "isotopically" or "radio-labeled" compound is a compound of the invention where one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature (*i.e.*, naturally occurring). Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to ^{3}H (also written as T for tritium), ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{18}F, ^{35}S, ^{36}Cl, ^{82}Br, ^{75}Br, ^{76}Br, ^{77}Br, ^{123}I, ^{124}I, ^{125}I and ^{131}I. The radionuclide that is incorporated in the instant radio-labeled compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* JAK labeling and competition assays, compounds that incorporate ^{3}H, ^{14}C, ^{82}Br, ^{125}I , ^{131}I, ^{35}S or will generally be most useful. For radio-imaging applications ^{11}C, ^{18}F, ^{125}I, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br or ^{77}Br will generally be most useful.

It is to be understood that a "radio-labeled" or "labeled compound" is a compound that has incorporated at least one radionuclide. In some embodiments the radionuclide is selected from the group consisting of ^{3}H, ^{14}C, ^{125}I , ^{35}S and ^{82}Br. In some embodiments, the compound incorporates 1, 2, or 3 deuterium atoms.

The present invention can further include synthetic methods for incorporating radio-isotopes into compounds of the invention. Synthetic methods for incorporating radio-isotopes into organic compounds are well known in the art, and an ordinary skill in the art will readily recognize the methods applicable for the compounds of invention.

A labeled compound of the invention can be used in a screening assay to identify/evaluate compounds. For example, a newly synthesized or identified compound (*i.e.*, test compound) which is labeled can be evaluated for its ability to bind a JAK by monitoring its concentration variation when contacting with the JAK, through tracking of the labeling. For example, a test compound (labeled) can be evaluated for its ability to reduce binding of another compound which is known to

bind to a JAK (*i.e.*, standard compound). Accordingly, the ability of a test compound to compete with the standard compound for binding to the JAK directly correlates to its binding affinity. Conversely, in some other screening assays, the standard compound is labeled and test compounds are unlabeled. Accordingly, the concentration of the labeled standard compound is monitored in order to evaluate the competition between the standard compound and the test compound, and the relative binding affinity of the test compound is thus ascertained.

Kits

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of JAK-associated diseases or disorders, such as cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of the invention. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results. The compounds of the Examples have been found to be JAK inhibitors according to at least one assay described *infra*.

EXAMPLES

Experimental procedures for compounds of the invention are provided below. Open Access Prep LC-MS Purification of some of the compounds prepared was performed on Waters mass directed fractionation systems. The basic equipment setup, protocols, and control software for the operation of these systems have been described in detail in literature. *See e.g.* "Two-Pump At Column Dilution Configuration for Preparative LC-MS", K. Blom, *J. Combi. Chem.*, 4, 295 (**2002**);

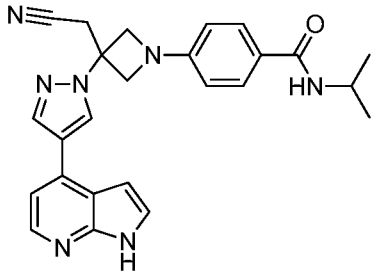
"Optimizing Preparative LC-MS Configurations and Methods for Parallel Synthesis Purification", K. Blom, R. Sparks, J. Doughty, G. Everlof, T. Haque, A. Combs, *J. Combi. Chem.*, 5, 670 (**2003**); and "Preparative LC-MS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Combi. Chem.*, 6, 874-883 (**2004**). The compounds separated were typically subjected to analytical liquid chromatography mass spectrometry (LCMS) for purity under the following conditions: Instrument; Agilent 1100 series, LC/MSD, Column: Waters Sunfire^{TM} C_{18} 5 μm, 2.1 x 5.0 mm, Buffers: mobile phase A: 0.025% TFA in water and mobile phase B: 0.025% TFA in acetonitrile; gradient 2% to 80% of B in 3 minutes with flow rate 1.5 mL/minute.

Some of the compounds prepared were also separated on a preparative scale by reverse-phase high performance liquid chromatography (RP-HPLC) with MS detector or flash chromatography (silica gel) as indicated in the Examples. Typical preparative reverse-phase high performance liquid chromatography (RP-HPLC) column conditions are as follows:

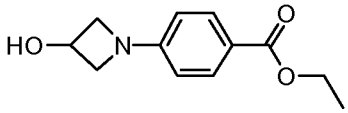
pH = 2 purifications: Waters Sunfire^{TM} C_{18} 5 μm, 19 x 100 mm column, eluting with mobile phase A: 0.1% TFA (trifluoroacetic acid) in water and mobile phase B: 0.1% TFA in acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [*See* "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with the with 30 x 100 mm column was 60 mL/minute.

pH = 10 purifications: Waters XBridge C_{18} 5 μm, 19 x 100 mm column, eluting with mobile phase A: 0.15% NH_4OH in water and mobile phase B: 0.15% NH_4OH in acetonitrile; the flow rate was 30 mL/minute, the separating gradient was optimized for each compound using the Compound Specific Method Optimization protocol as described in the literature [*See* "Preparative LCMS Purification: Improved Compound Specific Method Optimization", K. Blom, B. Glass, R. Sparks, A. Combs, *J. Comb. Chem.*, **6**, 874-883 (2004)]. Typically, the flow rate used with 30 x 100 mm column was 60 mL/minute.

Example 1. 4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide

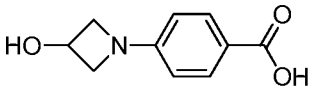


Step 1: ethyl 4-(3-hydroxyazetidin-1-yl)benzoate



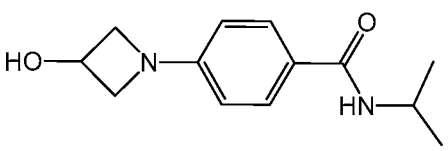
A mixture of ethyl 4-fluorobenzoate (0.841 g, 5.00 mmol, Aldrich: Cat.#102644), azetidin-3-ol hydrochloride (0.438 g, 4.00 mmol, Aldrich: Cat.#680079) and potassium carbonate (1.38 g, 9.98 mmol) in dimethyl sulfoxide (4 mL) was heated at 180 °C for 2 hours. After cooling, the mixture was diluted with ethyl acetate (50 mL), and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0-50%) to afford the desired product (0.643 g, 72.6%). LCMS $(M+H)^+$: m/z = 222.1.

Step 2: 4-(3-hydroxyazetidin-1-yl)benzoic acid



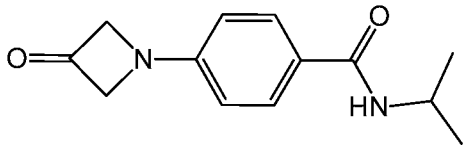
A mixture of 1-[4-(3-hydroxyazetidin-1-yl)phenyl]-2-methoxyethanone (1.33 g, 6.00 mmol) and lithium hydroxide monohydrate (504 mg, 12.0 mmol) in water (4 mL), methanol (3 mL) and THF (6 mL) was stirred at 40°C overnight. The mixture was neutralized with 3 N HCl aqueous solution (~4 mL) to pH about 7, extracted with ethyl acetate, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the crude product (1.10 g, 94.9%) which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 194.1.

Step 3: 4-(3-hydroxyazetidin-1-yl)-N-isopropylbenzamide



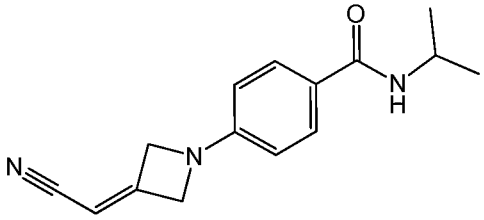
Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (4.64 g, 10.5 mmol, Aldrich: Cat.#226084) was added to a mixture of 4-(3-hydroxyazetidin-1-yl)benzoic acid (1.93 g, 10.0 mmol), 2-propanamine (4.26 mL, 50.0 mmol) and N,N-diisopropylethylamine (3.88 g, 30.0 mmol) in dichloromethylene (10 mL). The mixture was stirred at room temperature for 2 hours, and diluted with DCM. The mixture was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (gradient: 0-50%) to afford the desired product (2.21 g, 94.3%). LCMS $(M+H)^+$: m/z = 235.1.

Step 4: N-isopropyl-4-(3-oxoazetidin-1-yl)benzamide



To a cooled (-78°C) solution of oxalyl chloride (1.05 mL, 12.4 mmol) in dichloromethylene (20 mL) was added dropwise dimethyl sulfoxide (1.71 mL, 24.1 mmol). The mixture was stirred at -78°C for 10 minutes. Then a suspension of 4-(3-hydroxyazetidin-1-yl)-N-isopropylbenzamide (1.72 g, 7.34 mmol) in dichloromethylene (20 mL) was added. The mixture was stirred at -78°C for 1 hour, and then triethylamine (7.04 mL, 50.5 mmol) was added. The mixture was stirred at -78°C for an additional 1.5 hour. The mixture was washed with with aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The precipitates were washed with ether and collected by filtration to afford the desired product (1.32 g, 77%) which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 233.1.

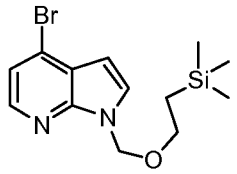
Step 5: 4-[3-(cyanomethylene)azetidin-1-yl]-N-isopropylbenzamide



To a cooled (at -6 to 0 °C) solution of 1.0 M potassium tert-butoxide in

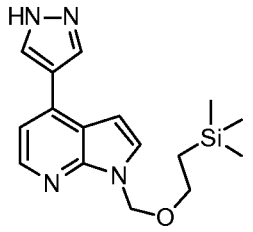
tetrahydrofuran (7.10 mL, 7.10 mmol) was added dropwise a solution of diethyl cyanomethylphosphonate (1.20 mL, 7.43 mmol, Aldrich: Cat.#D91705) in tetrahydrofuran (10.0 mL) over a period of 10 minuts and at -6 to 0 °C. The reaction was warmed and stirred at room temperature for 1 hour. The reaction mixture was re-cooled at -6 °C. To the reaction mixture was then added a solution of N-isopropyl-4-(3-oxoazetidin-1-yl)benzamide (1.30 g, 5.60 mmol) in tetrahydrofuran (10.0 mL) over a period of 10 minutes. During this time the temperature of the reaction mixture was between -5 to 0 °C. The reaction was allowed to warm to room temperature and was stirred for 3 hours. The reaction mixture was filtered through a pad of silica gel and washed with ethyl acetate. The filtrate was concentrated, and the residue was treated with ether. The precipitates formed were collected by filtration to give 0.60 g desired product. The mother liquid was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (gradient: 30-80%) to afford the desired product (0.21 g). the total product is 0.81 g (57%). LCMS $(M+H)^+$: m/z = 256.1.

Step 6: 4-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine



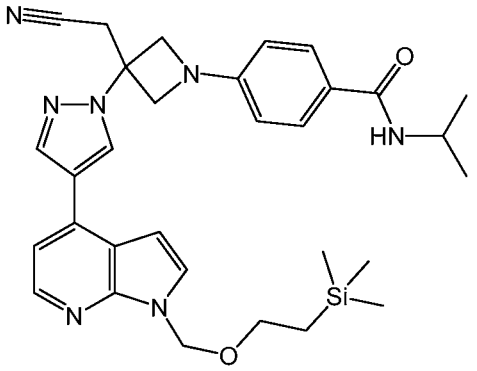
4-Bromo-1H-pyrrolo[2,3-b]pyridine (10.0 g, 0.0508 mol, Aldrich: Cat.#703451) was dissolved in N,N-dimethylformamide (100 mL) and cooled under nitrogen to 0 °C. Sodium hydride (3.00 g, 0.0750 mol, 60% disperson in mineral oil) was added portion-wise. The reaction was stirred for 10 minutes. [β-(Trimethylsilyl)ethoxy]methyl chloride (10.8 mL, 0.0609 mol, Aldrich: Cat.#238902) was added slowly to the reaction mixture, stirred at 0 °C for 45 minutes, and allowed to warm to room temperature. The solvent was removed under reduced pressure. The residue was diluted with ethyl ether (100 mL), and washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0 – 25%) to afford the desired product (16.04 g, 96.6%). LCMS $(M+H)^+$: m/z = 327.0/329.0

Step 7: 4-(1H-pyrazol-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine



A mixture of 4-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine (1.63 g, 4.98 mmol), *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (1.61 g, 5.48 mmol, Aldrich: Cat.#632732), tetrakis(triphenylphosphine)palladium(0) (288 mg, 0.249 mmol) and sodium carbonate (1.58 g, 14.9 mmol) in 1,4-dioxane (16.0 mL) and water (8.0 mL) was stirred at 110 °C for 2 hours. After cooling, the mixture was diluted with ethyl acetate, and washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was treated with ether, filtered and washed with ether to afford the desired product (1.08 g, 69%) which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 315.1.

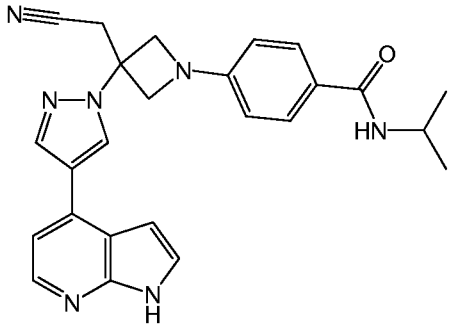
Step 8: 4-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide



A mixture of 4-(1H-pyrazol-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine (0.811 g, 2.58 mmol), 4-[3-(cyanomethylene)azetidin-1-yl]-N-isopropylbenzamide (0.625 g, 2.45 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (190 µL, 1.3 mmol) in acetonitrile (8 mL, 200 mmol) was heated at 50 °C for 1 hour. After cooling, the solvent was removed under reduced pressure. The residue was diluted with dichloromethylene, neutralized with 0.5 N HCl aqueous solution to about pH 7. The organic layer was washed with brine, dried over $MgSO_4$, filtered and

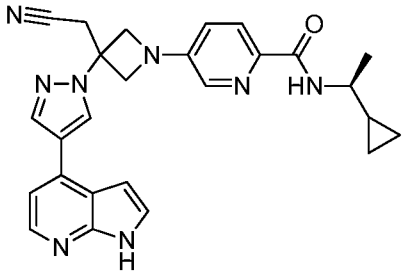
concentrated under reduced pressure to afford the desired product (1.40 g, 84.3%), which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 570.3.

Step 9: 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide



4-{3-(Cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide was dissolved in dichloromethylene (5 mL). To the solution was added trifluoroacetic acid (TFA) (2.5 mL). The mixture was stirred at room temperature for 1 hour. The volatiles were removed under reduced pressure. The residue was dissolved in methanol (10 mL). To the solution was added ethylenediamine (1 mL). The mixture was stirred at room temperature for 4 hours, and was purified by RP-HPLC (pH = 10) to afford the desired product (0.415 g). LCMS $(M+H)^+$: m/z = 440.1. The high purity (99.6%) of the product was obtained by re-crystallization from acetone-ether. ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.31 (d, J = 4.9 Hz, 1H), 8.15 (s, 1H), 8.11 (s, 1H), 7.70 (m, 2H), 7.39 (d, J = 3.4 Hz, 1H), 7.18 (d, J = 4.9 Hz, 1H), 6.70 (d, J = 3.4 Hz, 1H), 6.55 (m, 2H), 5.79 (d, J = 7.8 Hz, 1H), 4.47 (d, J = 8.3 Hz, 2H), 4.38 (d, J = 8.3 Hz, 2H), 4.27 (m, 1H), 3.45 (s, 2H), 1.25 (d, J = 6.7 Hz, 6H).

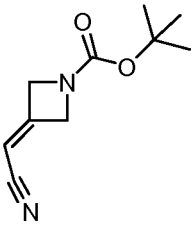
Example 2. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide



Step 1: 5-bromo-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide

(1S)-1-Cyclopropylethanamine (0.50 mL, 5.4 mmol, Alfa Aesar: Cat.#H27499) was added to a mixture of 5-bromopyridine-2-carboxylic acid (1.0 g, 5.0 mmol, Alfa Aesar: Cat.#B25675) in methylene chloride (30.0 mL), followed by benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (2.4 g, 5.4 mmol) and N,N-diisopropylethylamine (1.7 mL, 9.9 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with aqueous Na_2CO_3, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0 - 15%) to afford the desired product. LCMS $(M+H)^+$: m/z = 269.0/271.0.

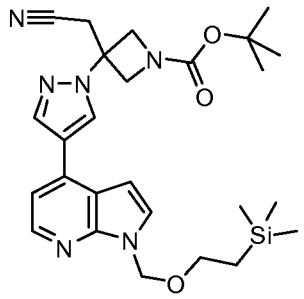
Step 2: tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate



To a solution of 1.0 M potassium tert-butoxide in tetrahydrofuran (30.7 mL, 0.0307 mol) at 0 °C was added dropwise a solution of diethyl cyanomethylphosphonate (5.20 mL, 0.0322 mol) in tetrahydrofuran (39.12 mL). The reaction was warmed to room temperature and then cooled at 0 °C again. To the reaction mixture was added a solution of *tert*-butyl 3-oxoazetidine-1-carboxylate (5.0 g, 0.029 mol, Aldrich: Cat.#696315) in tetrahydrofuran (7.82 mL). The reaction was allowed to warm to room temperature and stirred overnight. After quenched with water, the mixture was extracted with ethyl acetate. The combined organic layers

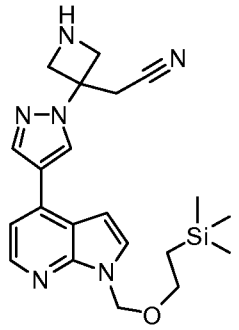
were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude mixture was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0 - 70%) to give the desired product (5.40 g, 95%). LCMS $(M+Na)^+$: m/z = 217.1.

Step 3: tert-butyl 3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate



A mixture of 4-(1H-pyrazol-4-yl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine (0.527 g, 1.68 mmol), *tert*-butyl 3-(cyanomethylene)azetidine-1-carboxylate (0.358 g, 1.84 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (135 µL, 0.903 mmol) in acetonitrile (4.0 mL) was heated at 50 °C for 1 hour. After cooling, the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate, neutralized with 0.5 N HCl aqueous solutions, washed brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product (0.85 g, quantitative) which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 509.3.

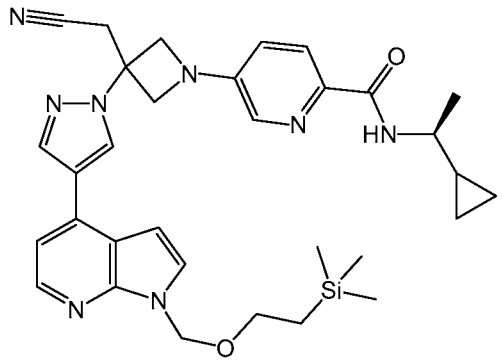
Step 4: {3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile



tert-Butyl 3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (0.85 g, 1.7

mmol) was dissolved in ethyl acetate (2 mL). To the solution was added 4.0 M hydrogen chloride in 1,4-dioxane (2.0 mL, 8.0 mmol). The mixture was stirred at room temperature for 3 hours. Ether was added, the mixture was centrifuged, and then the solvents were decanted. The residue was dried under vacuum to afford the desired product as HCl salt which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 409.2

Step 5: 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide



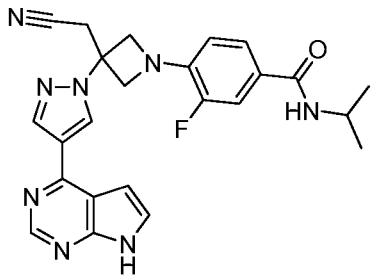
2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (91.1 mg, 0.146 mmol, Aldrich: Cat.#481084) was added to a mixture of {3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile hydrochloride (0.445 g, 1.00 mmol), 5-bromo-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide (0.273 g, 1.01 mmol), and cesium carbonate (0.971 g, 2.98 mmol) in toluene (10 mL) under N_2, followed by palladium acetate (32.2 mg, 0.143 mmol). The reaction mixture was stirred at 120 °C overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0 - 70%) to afford the desired product (0.350 g, 58.6%). LCMS $(M+H)^+$: m/z = 597.3.

Step 6: 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide

5-{3-(Cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-

pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide (0.350 g, 0.75 mmol) was dissolved in dichloromethylene (3 mL). To the solution was added TFA (1.5 mL). The mixture was stirred at room temperature for 2 hours. The volatiles were evaporated under reduced pressure. The residue was dissolved in methanol (5 mL), and ethylenediamine (1.0 mL) was added. The mixture was stirred at room temperature overnight, and was purified by RP-HPLC (pH=10) to afford the desired product. LCMS $(M+H)^+$: m/z = 467.3.

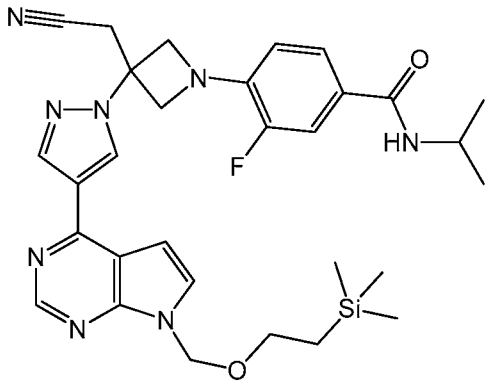
Example 3. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide



Step 1: 4-bromo-3-fluoro-N-isopropylbenzamide

2-Propanamine (1.2 mL, 14 mmol) was added to a mixture of 4-bromo-3-fluorobenzoic acid (2.09 g, 9.54 mmol, Alfa Aesar: Cat.#B25475) in methylene chloride (52.2 mL, 815 mmol), followed by benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (4.6 g, 10. mmol) and N,N-diisopropylethylamine (3.3 mL, 19 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0 - 20%) to afford the desired product (2.28 g, 91.8%). LCMS $(M+H)^+$: m/z = 260.0/262.0.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide



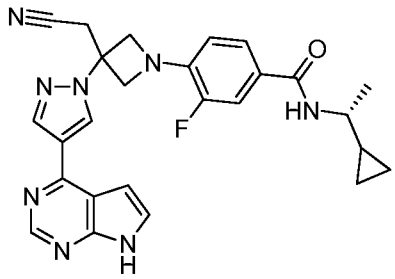
2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.32 g, 0.52 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (2.50 g, 5.18 mmol) (see WO 2009/114512), 4-bromo-3-fluoro-N-isopropylbenzamide (1.6 g, 6.2 mmol), and cesium carbonate (5.1 g, 16 mmol) in toluene (120 mL) under N_2, followed by palladium acetate (0.12 g, 0.52 mmol). The reaction mixture was stirred at 120 °C for 5 hours. After the reaction mixture was cooled to room temperature, the organic layer was separated from the solid. The solid was dissolved in water (50 mL), extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0 - 40%) to afford the desired product (2.20 g, 72.1%. LCMS $(M+H)^+$: m/z = 589.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide

Boron trifluoride etherate (2.0 mL, 16 mmol) was added to a solution of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide (2.20 g, 3.74 mmol) in acetonitrile (30.0 mL) at 0°C under N_2. The reaction mixture was stirred at room temperature overnight. The reaction was cooled to 0°C, water (5 mL) was added. After stirring at room temperature for 30 minutes, 5.0 M ammonium hydroxide in water (9 mL, 50 mmol) was added slowly at 0°C over a period of 5 minutes. Then the reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over

$MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with MeOH in dichloromethylene (0 - 5%) to afford the desired product (1.50 g, 63%) which was further purified by re-crystallization from acetone to afford the pure product (1.25 g, purity: 99.96%). The product was then converted to TFA salt. LCMS $(M+H)^+$: m/z = 459.2. ^1H NMR (300 Hz, DMSO-d_6): δ 12.73 (s, 1H), 9.11 (s, 1H), 8.85 (s, 1H), 8.57 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 2.5 Hz, 1H), 7.64 (s, 1H), 7.60 (t, J = 2.5 Hz, 1H), 7.27 (d, J = 2.5 Hz, 1H), 6.72 (t, J = 9.0 Hz, 1H), 4.66 (d, J = 7.0 Hz, 2H), 4.41 (d, J = 7.0 Hz, 2H), 4.04 (m, 1H), 3.73 (s, 2H), 1.12 (d, J = 6.5 Hz, 6H).

Example 4. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide



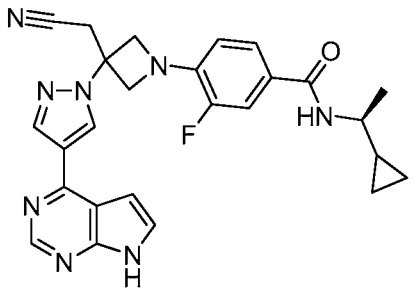
Step 1: 4-bromo-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide

N,N-Diisopropylethylamine (0.92 mL, 5.3 mmol) was added to a mixture of 4-bromo-3-fluorobenzoic acid (0.58 g, 2.6 mmol), (1R)-1-cyclopropylethanamine (0.27 mL, 2.9 mmol, Alfa Aesar: Cat.#H26902) and benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (1.3 g, 2.9 mmol) in methylene chloride (5.8 mL, 91 mmol). The reaction mixture was stirred at room temperature for 30 minutes, worked up with aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0 - 10%) to afford the desired product (0.71 g, 94%). LCMS $(M+H)^+$: m/z = 286.0/288.0.

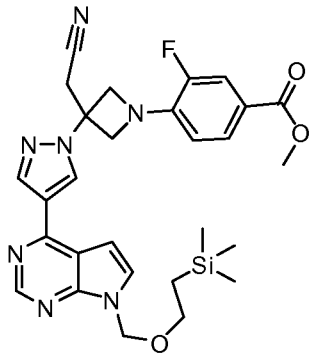
Step 2: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide

This compound was prepared as TFA salt by using procedures analogous to those described for the synthesis of Example 3, Step 2-3 starting from {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride and 4-bromo-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide (from Step 1, above). LCMS $(M+H)^+$: m/z = 485.2. ^{1}H NMR (400 MHz, DMSO- d_6): δ 12.67 (s, 1H), 9.01 (s, 1H), 8.88 (s, 1H), 8.46 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 2.5 Hz, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 7.17 (d, J = 2.5 Hz, 1H), 6.61 (t, J = 8.4 Hz, 1H), 4.53 (d, J = 8.0 Hz, 2H), 4.28 (d, J = 8.0 Hz, 2H), 3.63 (s, 2H), 3.28 (m, 1H), 1.04 (d, J = 6.5 Hz, 6H), 0.82 (m, 1H), 0.30 (m, 1H), 0.20 (m, 1H), 0.06 (m, 1H), 0.01 (m, 1H).

Example 5. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]-3-fluorobenzamide



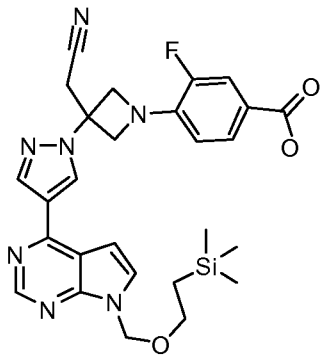
Step 1: methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoate



2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.11 g, 0.18 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (0.86 g, 1.8 mmol), methyl 4-bromo-3-fluorobenzoate (0.50 g, 2.1 mmol, Combi-Blocks: Cat.#CA-4107), and cesium carbonate (1.7 g, 5.4 mmol) in toluene (25.0 mL) under N_2, followed by palladium acetate (0.040 g, 0.18 mmol). The reaction mixture was

stirred at 120°C for 5 hours. The reaction mixture was diluted with ethyl acetate, filtered, and concentrated under reduced pressure to afford the desired crude product (1.06 g) which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 562.3.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoic acid



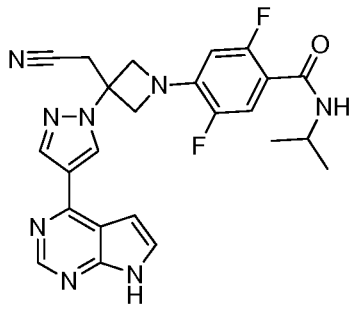
Lithium hydroxide monohydrate (0.21 g, 5.0 mmol) was added to a mixture of methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoate (1.06 g) in methanol (15.0 mL) and water (3.0 mL). The reaction mixture was stirred at 40 °C overnight. The mixture was adjusted to pH 3 with aqueous HCl (1.00 N), and concentrated under reduced pressure to remove methanol. The solid formed was filtered and washed with water, and dried under reduced pressure to afford the crude product (0.95 g) which was directly used in next step reaction without further purification. LCMS $(M+H)^+$: m/z = 548.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]-3-fluorobenzamide

A mixture of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoic acid (20.0 mg, 0.0365 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (19 mg, 0.044 mmol) in dichloromethylene (1.0 mL) was added to a mixture of (1S)-1-cyclopropylethanamine (4.7 mg, 0.055 mmol) and triethylamine (15 μL, 0.11 mmol) in methylene chloride (0.6 mL). The reaction mixture was stirred at room temperature overnight. The

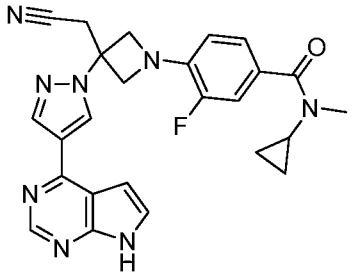
reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with dichloromethylene (2 x 2 mL). The combined organic layers were washed with water (1 mL), concentrated and dried under reduced pressure. The residue was treated with methylene chloride (1.3 mL) and trifluoroacetic acid (0.6 mL), and stirred at room temperature for 1.5 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in methanol (1.3 mL). Ethylenediamine (0.086 mL, 1.3 mmol) were added. The reaction mixture was stirred at room temperature for 2 hours, and purified by RP-HPLC (pH = 10) (the conditions are already mention before the examples) to afford the desired product. LCMS $(M+H)^+$: m/z = 485.2.

Example 6. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-isopropylbenzamide



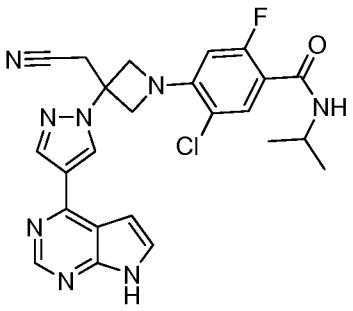
This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 1-3 starting from 4-chloro-2,5-difluorobenzoic acid (Aldrich: Cat.#443824), 2-propanamine and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 477.2. ^1H NMR (400 MHz, DMSO- d_6): δ 12.61 (s, 1H), 9.08 (s, 1H), 8.84 (s, 1H), 8.57 (s, 1H), 7.80 (m, 2H), 7.37 (dd, J = 13.0, 7.0 Hz, 1H), 7.23 (m, 1H), 6.63 (dd, J = 13.0, 8.0 Hz, 1H), 4.51 (d, J = 9.0 Hz, 2H), 4.42 (d, J = 9.0 Hz, 2H), 3.78 (s, 2H), 4.03 (m, 1H), 1.13 (d, J = 6.5 Hz, 6H).

Example 7. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-cyclopropyl-3-fluoro-N-methylbenzamide



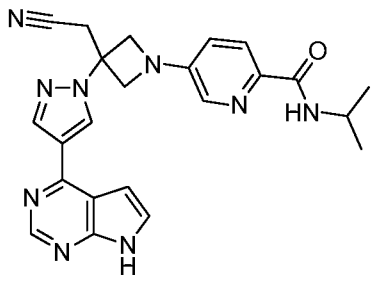
This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 1-3 starting from 4-bromo-3-fluorobenzoic acid, N-methylcyclopropanamine hydrochloride (J&W PharmLab: Cat.#20-0433S) and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 471.2. ^{1}H NMR (400 MHz, DMSO-D_6): δ 12.83 (s, 1H), 9.17 (s, 1H), 8.91 (s, 1H), 8.60 (s, 1H), 7.85 (s, 1H), 7.33 (m, 3H), 6.71 (t, J = 9.0 Hz, 1H), 4.66 (d, J = 8.0 Hz, 2H), 4.41 (d, J = 8.0 Hz, 2H), 3.79 (s, 2H), 2.97 (m, 1H), 2.93 (s, 3H), 0.59 (m, 2H), 0.42 (m, 2H).

Example 8. 5-Chloro-4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-isopropylbenzamide



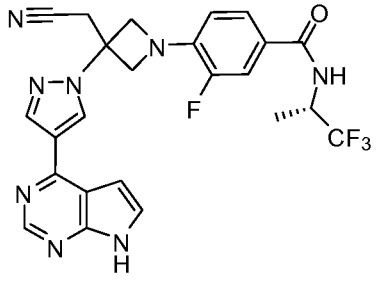
This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 1-3 starting from 4,5-dichloro-2-fluorobenzoic acid (Ark Pharm, Inc. , Cat. #: AK-29091), 2-propanamine and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 493.2/495.2. ^{1}H NMR (400 MHz, DMSO- d_6): δ 12.65 (s, 1H), 9.09 (s, 1H), 8.85 (s, 1H), 8.56 (s, 1H), 7.86 (dd, J = 8.0, 2.5 Hz, 1H), 7.78 (m, 1H), 7.52 (d, J = 7.0 Hz, 1H), 7.23 (m, 1H), 6.64 (d, J = 12.0 Hz, 1H), 4.77 (d, J = 9.0 Hz, 2H), 4.51 (d, J = 9.0 Hz, 2H), 3.75 (s, 2H), 4.00 (m, 1H), 1.12 (d, J = 6.5 Hz, 6H).

Example 9. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyridine-2-carboxamide



This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 1-3 starting from 5-bromopyridine-2-carboxylic acid, 2-propanamine and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 442.2. ^{1}H NMR (400 MHz, DMSO- d_6): δ 12.82 (s, 1H), 9.12 (s, 1H), 8.88 (s, 1H), 8.59 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.83 (m, 1H), 7.28 (m, 1H), 7.10 (dd, J = 8.0, 3.0 Hz, 1H), 4.66 (d, J = 8.0 Hz, 2H), 4.41 (d, J = 8.0 Hz, 2H), 3.78 (s, 2H), 4.05 (m, 1H), 1.16 (d, J = 6.5 Hz, 6H).

Example 10. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide



Step 1: 4-bromo-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide

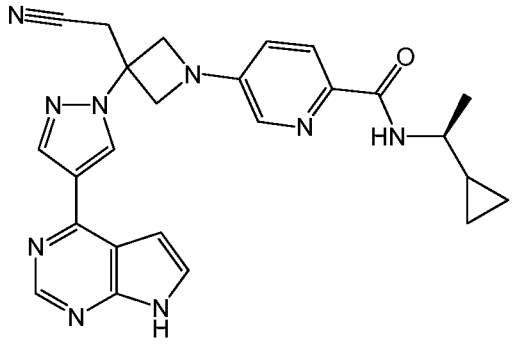
(2S)-1,1,1-Trifluoropropan-2-amine hydrochloride (0.068 g, 0.46 mmol) (ACS Scientific Inc., Cat. # 2-01-6) was added to a mixture of 4-bromo-3-fluorobenzoic acid (0.100 g, 0.457 mmol) and N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.26 g, 0.68 mmol) in methylene chloride (2.50 mL), followed by N,N-diisopropylethylamine (0.16 mL, 0.91 mmol). The reaction

mixture was stirred at room temperature overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with methylene chloride (3x20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-20%) to afford the desired product. LCMS $(M+H)^+$: m/z = 314.0/316.0.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide

This compound was prepared as TFA salt by using procedures analogous to those described for the synthesis of Example 3, Step 2-3 starting from {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride and 4-bromo-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide (from Step 1, above). LCMS $(M+H)^+$: m/z = 513.2. ^1H NMR (300 MHz, DMSO- d_6): δ 12.64 (s, 1H), 9.08 (s, 1H), 8.83 (s, 1H), 8.61 (d, J = 8.5 Hz, 1H), 8.57 (s, 1H), 7.79 (m, 1H), 7.70 (s, 1H), 7.66 (m, 1H), 7.23 (d, J = 2.3 Hz, 1H), 6.76 (t, J = 8.5 Hz, 1H), 4.80 (m, 1H), 4.68 (d, J = 8.0 Hz, 2H), 4.53 (d, J = 8.0 Hz, 2H), 3.76 (s, 2H), 1.32 (d, J = 7.0 Hz, 3H).

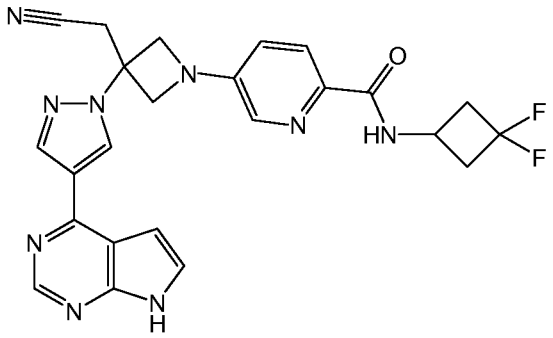
Example 11. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide



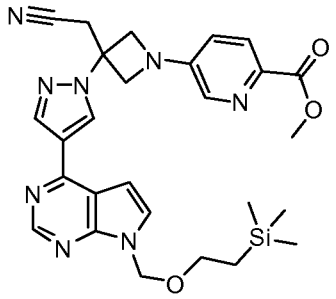
This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 2-3 starting from 5-bromo-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide (Example 2, Step 1) and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 468.2. ^1H NMR (400 MHz, DMSO- d_6): δ 12.60 (s, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.60 (s,

1H), 8.26 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 3.0 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.84 (m, 1H), 7.28 (m, 1H), 7.12 (dd, J = 8.0, 3.0 Hz, 1H), 4.68 (d, J = 8.0 Hz, 2H), 4.43 (d, J = 8.0 Hz, 2H), 3.80 (s, 2H), 3.39 (m, 1H), 1.12 (t, J = 7.0 Hz, 3H), 1.05 (m, 1H), 0.45 (m, 1H), 0.38 (m, 1H), 0.22 (m, 1H).

Example 12. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(3,3-difluorocyclobutyl)pyridine-2-carboxamide



Step 1: methyl 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyridine-2-carboxylate



A mixture of 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (660 mg, 1.1 mmol), {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile hydrochloride (4.76 g, 10.7 mmol), methyl 5-bromopicolinate (3.00 g, 13.9 mmol), palladium acetate (240 mg, 1.1 mmol) and cesium carbonate (10 g, 32 mmol) in toluene (120 mL) was de-gassed and recharged with nitrogen for three times. The reaction mixture was stirred at 100°C overnight. After cooling the reaction mixture was quenched with water, and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with MeOH in dichloromethylene (0 - 5%) to afford the desired product (3.70 g, 63.6%). LCMS $(M+H)^+$: m/z = 545.3.

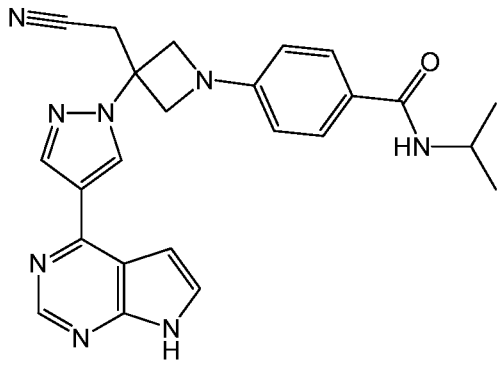
Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyridine-2-carboxylic acid

A mixture of lithium hydroxide monohydrate (0.87 g, 21 mmol) and methyl 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyridine-2-carboxylate (3.70 g, 6.79 mmol) in methanol (10.0 mL) and water (5.0 mL) was stirred at room temperature overnight. The mixture was adjusted to pH 3 with aqueous HCl (1.0 N), and concentrated under reduced pressure to remove methanol. The solid formed was filtered and washed with water, and dried under reduced pressure to afford the crude product. LCMS $(M+H)^+$: m/z = 531.1.

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(3,3-difluorocyclobutyl)pyridine-2-carboxamide

A mixture of benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (60.0 mg, 0.14 mmol), 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyridine-2-carboxylic acid (48.4 mg, 0.0913 mmol), 3,3-difluorocyclobutanamine hydrochloride (20. mg, 0.14 mmol, Molbridge: Cat.#MB00001399) and N,N-diisopropylethylamine (64 μL, 0.36 mmol) in methylene chloride (2 mL) was stirred at room temperature overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with dichloromethylene (2 x 2 mL). The combined organic layers were washed with water (1 mL), concentrated and dried under reduced pressure. The residue was dissolved in dichloromethylene (1 mL) and trifluoroacetic acid (0.5 mL). The mixture was stirred at room temperature for 1.5 hours, and concentrated under reduced pressure. The residue was dissolved in methanol (2.5 mL). Ethylenediamine (0.21 mL, 3.2 mmol) were added. The reaction mixture was stirred at room temperature for 2 hours, and purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 490.1. ^1H NMR (300 MHz, DMSO-d_6): δ 12.50 (br, 1H), 9.01 (s, 1H), 8.93 (d, J = 7.8 Hz, 1H), 8.76 (s, 1H), 8.50 (s, 1H), 7.89 (d, J = 2.7 Hz, 1H), 7.81 (d, J = 8.6 Hz, 1H), 7.70 (dd, J = 3.4, 2.5 Hz, 1H), 7.15 (dd, J = 3.5, 1.5 Hz, 1H), 7.04 (dd, J = 8.6, 2.8 Hz, 1H), 4.63 (d, J = 9.0 Hz, 2H), 4.36 (d, J = 8.9 Hz, 2H), 4.23 (m, 1H), 3.73 (s, 2H), 2.80 (m, 4H).

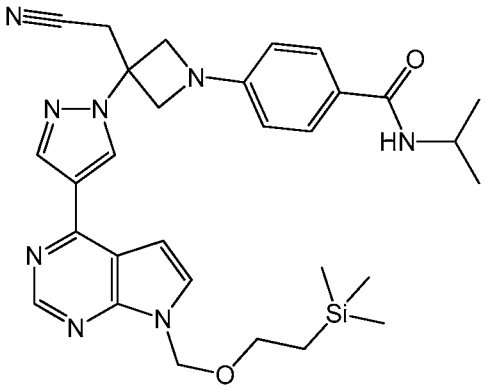
Example 13. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-isopropylbenzamide



Step 1: 4-bromo-N-isopropylbenzamide

A solution of 4-bromobenzoic acid (4.00 g, 19.9 mmol, Aldrich: Cat.#108510) and thionyl chloride (10.0 mL, 137 mmol) was heated by microwave irradiation at 100 °C for 1 h, turning the heterogeneous solution to a homogeneous solution. The volatiles were removed *in vacuo* and the residue was azeotropically washed with dry acetonitrile several times (20 mL x 4) to remove excess thionyl chloride. The residue was dissolved in anhydrous methylene chloride (40 mL) and cooled to 0 °C prior to the addition of 2-propanamine (8.0 mL, 94 mmol, 99.5% pure Aldrich [75-31-0]). After 1 hour, the reaction mixture was diluted with methylene chloride (20 mL) and quenched with H_2O (5 mL). The layers were separated and the organic layer was washed with H_2O (1 x 5 mL), saturated $NaHCO_3$ (1 x 5 mL), H_2O (1 x 5 mL), 1 N HCl (3 x 5 mL), H_2O (1 x 5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the desired product (4.50 g, 93 % yield) which was used directly in the next step without further purification. LCMS $(M+H)^+$: m/z = 242/244.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide



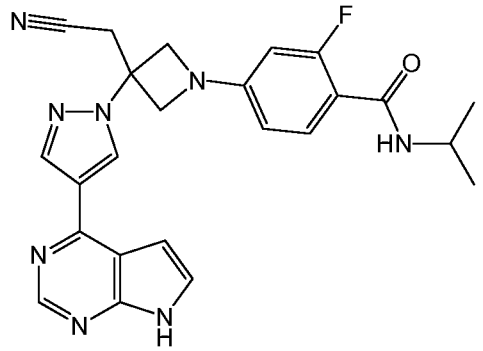
A mixture of 4-bromo-*N*-isopropylbenzamide (1.82 g, 7.52 mmol), {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile hydrogen chloride (2.23 g, 5.00 mmol), palladium acetate (78 mg, 0.35 mmol, Aldrich [3375-31-3]), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (405 mg, 0.700 mmol, Aldrich [161265-03-8]), and cesium carbonate (3.03 g, 9.30 mmol) in toluene (22 mL) was de-gassed and purged several times with N_2 (g) prior to heating at 105 °C in a sealed vial for 2 days. Upon cooling to room temperature the reaction mixture was filtered through a pad of celite, concentrated in-vacuo and purified by flash chromatography on a silica gel column eluting with MeOH in methylene chloride (0 - 5%) to afford the desired product (1.74 g, 61 % yield). LCMS $(M+H)^+$: m/z = 571.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide

4-{3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-isopropylbenzamide (1.74 g, 3.05 mmol) was dissolved in methylene chloride (5.0 mL) and trifluoroacetic acid (5.0 mL, 26 mmol) and stirred at room temperature After 4 hours, LC/MS data indicated that the reaction was complete and the desired product was formed (LCMS $(M+H)^+$: m/z = 471.3). The volatiles were removed *in vacuo* and the residue was azeotropically washed with acetonitrile several times (4 x 10 mL) to remove the excess TFA. The residue was dissolved in methanol (15 mL) and to this was added 14.8 M ammonium hydroxide in H_2O (3.0 mL, 44 mmol) and ethylenediamine (0.10 mL, 1.5 mmol) and the resulting solution was stirred at room temperature for 3 hours to afford the desired product. The product was further precipitated out as a white solid by the addition of H_2O (15 mL) and the heterogeneous solution was stirred for 30

minutes prior to pouring into water (60 mL). The precipitate was filtered off, washed with water (2 x 10 mL), and dried under high vacuum to afford the desired product (1.05 g, 78 % yield). LCMS $(M+H)^+$: m/z = 441.1. ^1H NMR (400 MHz, CD_3OD): δ 8.78 (s, 1H), 8.66 (s, 1H), 8.42 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 4.0 Hz, 1H), 7.00 (d, J = 4.0 Hz, 1H), 6.64 (t, J = 8.5 Hz, 2H), 4.55 (d, J = 8.0 Hz, 2H), 4.40 (d, J = 8.0 Hz, 2H), 4.19 (m, 1H), 3.62 (s, 2H), 1.22 (d, J = 7.0 Hz, 6H).

Example 14. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-isopropylbenzamide

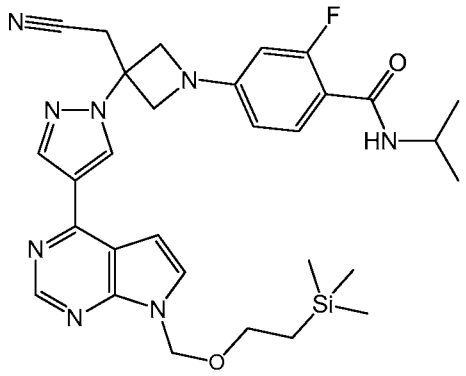


Step 1: 4-bromo-2-fluoro-N-isopropylbenzamide

A solution of 4-bromo-2-fluorobenzoic acid (1.50 g, 6.85 mmol, Combi-Blocks: Cat.# CA-4096), *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (2.86 g, 7.53 mmol), and *N,N*-diisopropylethylamine (2.4 mL, 14 mmol) in methylene chloride (20. mL) was stirred for 10 minutes. 2-Propanamine (2.3 mL, 27 mmol) was then added and stirring was continued for 1.5 hours LC/MS data indicated that the major reaction component was the desired product. The reaction mixture was diluted with methylene chloride (40 mL) and H_2O (3 mL). The layers were separated and the organic layer was washed with water (3 x 3 mL) and 1N HCl (3 x 3 mL). The combined aqueous phases were extracted with methylene chloride (5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The crude product was purified by flash chromatography on a silica gel column eluting with ethyl acetate in hexanes (0 - 15%) to afford the desired product. LCMS $(M+H)^+$: m/z = 260.0/262.0.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-

isopropylbenzamide



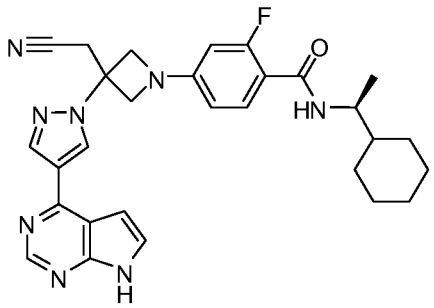
A mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile [1.0]-hydrogen chloride (1.71 g, 3.84 mmol), cesium carbonate (2.6 g, 8.1 mmol), palladium acetate (94 mg, 0.42 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (470 mg, 0.81 mmol), and 4-bromo-2-fluoro-*N*-isopropylbenzamide (1.00 g, 3.84 mmol) in toluene (20 mL, 200 mmol) was de-gassed, purged with N_2 (g) three times, and heated to 100 °C overnight. Upon cooling to room temperature, the crude reaction mixture was filtered through a pad of celite and the inorganics were washed with ethyl acetate (5 x 10 mL). The filtrate was concentrated in-vacuo and purified by flash chromatography on a silica gel column eluting with methanol in methylene chloride (0 - 5%) to afford the desired product (1.6 g, 70% yield). LCMS $(M+H)^+$: m/z = 589.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-isopropylbenzamide

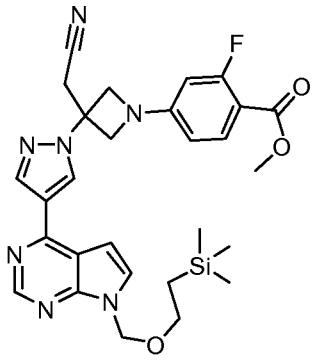
4-{3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-isopropylbenzamide (0.7 g, 1.19 mmol) was dissolved in methylene chloride (5.0 mL) and to this was added trifluoroacetic acid (5.0 mL) and the solution was stirred at room temperature for 1 hour. LC/MS data indicated that the main reaction component was the desired product (LCMS $(M+H)^+$: m/z = 489.2). The volatiles were removed in-vacuo and the residue was azeotropically washed with acetonitrile (3 x 10 mL). The resulting residue was dissolved in methanol (4 mL) followed by the addition of ethylenediamine (400 μL) and ammonium hydroxide (1.2 mL). After stirring at room temperature for 2 hours, LC/MS data indicated that the main reaction component was

the desired product. The crude reaction mixture was purified by RP-HPLC (pH = 2) to afford the desired product as TFA salt. LCMS $(M+H)^+$: m/z = 459.2. ^{1}H NMR (500 MHz, CD_3OD): δ 9.09 (s, 1H), 8.90 (s, 1H), 8.56 (s, 1H), 7.85 (d, *J* = 3.7 Hz, 1H), 7.66 (t, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 3.8 Hz, 1H), 6.47 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.39 (dd, *J* = 13.5, 2.2 Hz, 1H), 4.61 (d, *J* = 8.8 Hz, 2H), 4.44 (d, *J* = 8.8 Hz, 2H), 4.22-4.13 (m, 1H), 3.68 (s, 2H), 1.23 (d, *J* = 6.6 Hz, 6H).

Example 15. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclohexylethyl]-2-fluorobenzamide



Step 1: Methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoate



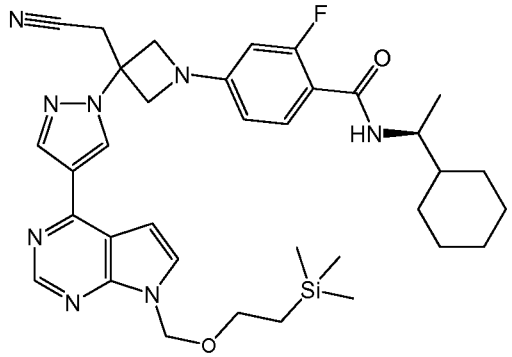
A mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (1.8 g, 3.7 mmol), methyl 4-bromo-2-fluorobenzoate (1.00 g, 4.29 mmol) (Combi-Blocks: Cat.#CA-4291), cesium carbonate (3.6 g, 11 mmol), palladium acetate (0.10 g, 0.44 mmol), and 9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine (0.54 g, 0.93 mmol) in dry toluene (20 mL) was de-gassed and purged several times with nitrogen, and heated at 90 °C in a sealed vial for 14 hours with stirring. Upon cooling to room temperature, the reaction mixture was filtered through a pad of celite, concentrated in-vacuo and purified by flash chromatography on a silica gel column with hexanes-ethyl

acetate to afford the desired product (1.72 g, 82% yield). LCMS $(M+H)^+$: m/z = 562.2.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoic acid

To a solution of methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoate (1.22 g, 2.17 mmol) in tetrahydrofuran (10 mL) was added a solution of lithium hydroxide (0.21 g, 8.8 mmol) in water (9.8 mL). The reaction mixture was then stirred at 35 °C for 24 hours. The reaction mixture was diluted with water (5 mL) and pH was adjusted to ~ 4 with 1 N HCl, extracted with ethyl acetate. The organic fraction was washed with water (1x), brine (1x), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The solid was then triturated with methylene chloride - methanol (95:5), filtrated to afford the desired product (0.917 g, 77.1%). LCMS $(M+H)^+$: m/z = 562.2.

Step 3: 4-{3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclohexylethyl]-2-fluorobenzamide



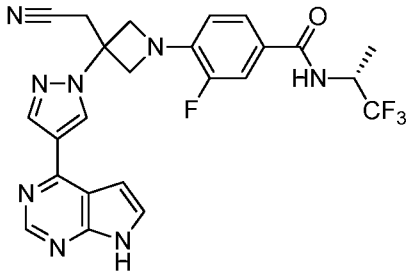
The 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoic acid (0.015 g, 0.027 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.016 g, 0.042 mmol), and (1S)-1-cyclohexylethanamine (0.0080 mL, 0.055 mmol, Aldrich: Cat.#336513) in dry 1,2-dichloroethane (0.501 mL) (not all in solution) was stirred for 30 minutes at 60 °C, then 14 hours at room temperature (all in solution). LC/MS data showed that the reaction was complete and

the desired product was formed. The product was used as is without further purification. LCMS $(M+H)^+$: m/z = 657.3.

Step 4: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclohexylethyl]-2-fluorobenzamide

To the above reaction mixture in 1,2-dichloroethane (0.5mL) was added trifluoroacetic acid (0.200 mL) and stirred for 1.5 hours. The volatiles were removed *in-vacuo* and the residue was azeotropically washed with acetonitrile (3x). The resulting residue was redissolved in methanol (0.500 mL), added ethylenediamine (0.049 mL, 0.74 mmol) and was stirred for 40 minutes, concentrated under reduced pressure. The crude product was then purified by LC/MS (pH = 2) to give the desired product as TFA salt (0.009g, 40% yield). LCMS $(M+H)^+$: m/z = 527.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.36 (s, 1H), 8.98 (s, 1H), 8.76 (s, 1H), 8.50 (s, 1H), 7.71 – 7.65 (m, 1H), 7.51 (t, J = 8.5 Hz, 1H), 7.48 (dd, J = 8.5, 4.3 Hz, 1H), 7.14 (d, J = 1.9 Hz, 1H), 6.43 (s, 1H), 6.41 (dd, J = 4.8, 2.0 Hz, 1H), 4.57 (d, J = 8.8 Hz, 2H), 4.31 (d, J = 8.8 Hz, 2H), 3.84 – 3.76 (m, 1H), 3.75 (s, 2H), 1.77 – 1.65 (m, 4H), 1.60 (d, J = 11.4 Hz, 1H), 1.44 – 1.30 (m, 1H), 1.23 – 1.08 (m, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.88 – 0.99 (m, 2H).

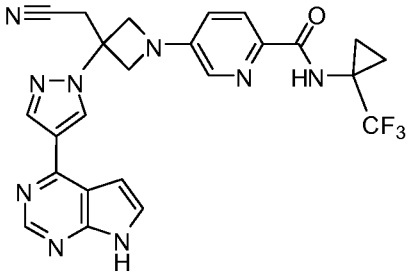
Example 16. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide



This compound was prepared by using procedures analogous to those described for the synthesis of Example 5, Step 3 starting from 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoic acid and (2R)-1,1,1-trifluoropropan-2-amine hydrochloride. LCMS $(M+H)^+$: m/z = 513.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66 (br, 1H), 9.11 (s, 1H), 8.86 (s, 1H), 8.64 (d, J = 8.9 Hz, 1H), 8.58 (s, 1H), 7.80

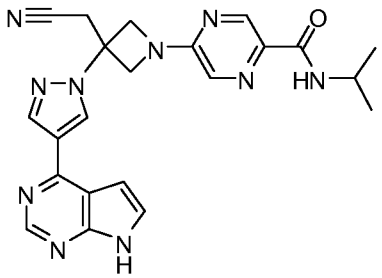
(br, 1H), 7.71 (s, 1H), 7.69 (dd, J = 4.0, 1.6 Hz, 1H), 7,26 (br, 1H), 6.78 (t, J = 8.7 Hz, 1H), 4.89-4.78 (m, 1H), 4.71 (d, J = 7.7 Hz, 2H), 4.45 (dd, J = 9.4, 1.8 Hz, 2H), 3.78 (s, 2H), 1.35 (d, J = 7.0 Hz, 3H).

Example 17. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

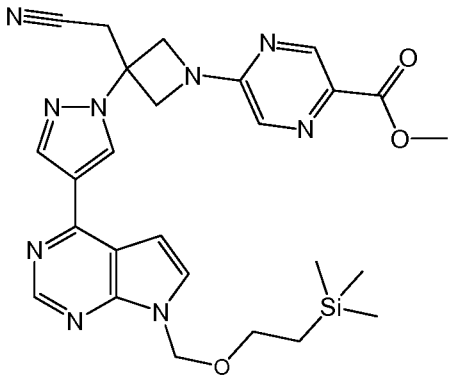


This compound was prepared by using procedures analogous to those described for the synthesis of Example 12, Step 3 starting from 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyridine-2-carboxylic acid (Example 12, Step 2) and 1-(trifluoromethyl)cyclopropanamine (Oakwood Products, Inc., Cat. #: 038175). LCMS $(M+H)^+$: m/z = 508.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.69 (br, 1H), 9.12 (s, 1H), 9.11 (d, J = 2.9 Hz, 1H), 8.87 (s, 1H), 8.59 (s, 1H), 7.95 (d, = 2.7 Hz, 1H), 7.89 (d, J = 8.6 Hz, 1H), 7.84-7.80 (br, 1H), 7.26 (dd, J = 2.1, 1.3 Hz, 1H), 7.11 (dd, J = 8.7, 2.8 Hz, 1H), 4.70 (d, J = 9.1 Hz, 2H), 4.44 (d, J = 9.2 Hz, 2H), 3.80 (s, 2H), 1.28 (m, 2H), 1.17 (m, 2H).

Example 18. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide



Step 1: methyl 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate



(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (0.065 g, 0.10 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (0.50 g, 1.0 mmol), methyl 5-chloropyrazine-2-carboxylate (0.18 g, 1.0 mmol)(Ark Pharm, Inc., Cat. #: AK-23920), and cesium carbonate (1.0 g, 3.1 mmol) in toluene (15.0 mL) under nitrogene, followed by palladium acetate (0.023 g, 0.10 mmol). The reaction mixture was stirred at 120°C for 3 h. After cooled to r.t., the reaction mixture was filtered throught a pad of celite, washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethane (0-70%) to afford the desired product (0.31 g, 55%). LCMS $(M+H)^+$: m/z = 546.3.

Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid

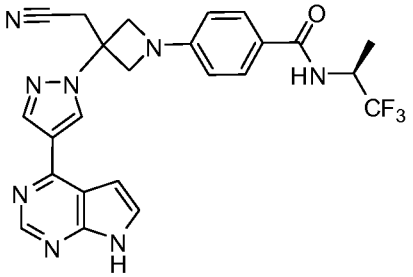
A mixture of methyl 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]-methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate (0.31 g, 0.57 mmol), lithium hydroxide monohydrate (0.060 g, 1.4 mmol) in methanol (6.0 mL) and water (2.5 mL) was stirred at 30°C overnight. The mixture was adjuested to pH = 4 with aqueous HCl, and concentrated under reduced pressure to remove MeOH. The resulted solid was filtered, washed with water and ether, and then dried in vacuum to afford the desired product (0.25 g, 83%). LCMS $(M+H)^+$: m/z = 532.3

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide

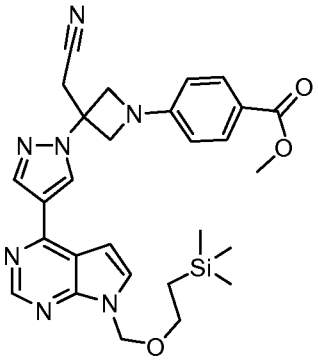
Triethylamine (15 μL, 0.11 mmol) was added to a mixture of 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid (19.4 mg, 0.0365 mmol) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (19 mg, 0.044 mmol) and 2-propanamine (3.2 mg, 0.055 mmol) in methylene chloride (1.3 mL). The reaction mixture was stirred at r.t. overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with methylene chloride (2 x 2 mL). The combined organic layers were washed with water (1 mL) and concentrated under reduced pressure. The residue was used for next step without further purification. LCMS $(M+H)^+$: m/z = 573.3.

Methylene chloride (1.3 mL) and trifluoroacetic Acid (0.6 mL) were added to the above intermediate. The reaction mixture was stirred at r.t. for 1.5 h. The mixture was concentrated under reduced pressure. The residue was dissolved in methanol (1.3 mL). To the solution was added ethylenediamine (0.086 mL). The reaction mixture was stirred at r.t. for 2 h., and purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 443.2. ^1H NMR (400 MHz, DMSO-d_6): δ 12.15 (br, 1H), 8.97 (s, 1H), 8.68 (s, 1H), 8.63 (d, J = 1.2 Hz, 1H), 8.46 (s, 1H), 8.12 (d, = 8.4 Hz, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.60 (dd, J = 3.3, 2.4 Hz, 1H), 7.07 (dd, J = 3.4, 1.7 Hz, 1H), 4.81 (d, J = 9.8 Hz, 2H), 4.53 (d, J = 9.6 Hz, 2H), 4.13-4.02 (m, 1H), 3.78 (s, 2H), 1.14 (d, J = 6.8 Hz, 6H).

Example 19. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]benzamide bis(trifluoroacetate)



Step 1: methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoate



A mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (0.250 g, 0.518 mmol), methyl 4-bromobenzoate (0.13 g, 0.60 mmol, Aldrich: Cat.#407593), cesium carbonate (0.39 g, 1.2 mmol), palladium acetate (0.014 g, 0.060 mmol), 9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine (0.070 g, 0.12mmol) in dry toluene (3 mL) was de-gassed and purged several times with nitrogen, and heated at 100 °C in a sealed tube for 14 hours with stirring. Upon cooling to room temperature the reaction mixture was filtered through a pad of celite. The filtrate was washed with water (1x), brine (1x), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on a silica gel column with ethyl acetate in hexane to afford the desired product (0.240 g, 87%). LCMS $(M+H)^+$: m/z = 544.2.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoic acid

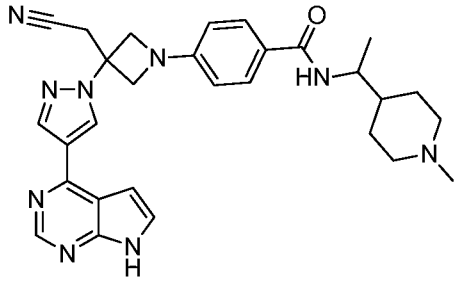
To a solution of methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)-ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoate (0.9 g, 2 mmol) in tetrahydrofuran (8 mL) was added a solution of lithium hydroxide (0.16 g, 6.7 mmol) in water (7.4 mL). The reaction mixture was then stirred at 35 °C. The progress of reaction was monitored by LC/MS. After 46 hours, LC/MS data indicated that the main component of the reaction was the desired product LCMS m/z = 530.2. The reaction mixture was diluted with water (5 mL), pH was adjusted to ~ 4 with 1N HCl, and was extracted with ethyl acetate. Organic fraction was then washed water (1x), brine (1x), dried over sodium sulfate and then concentrated in-vacuo. The crude product was purified by flash chromatography on a silica gel column with methanol in methylene chloride to give the desired product

(0.450g, 50%). LCMS $(M+H)^+$: m/z = 530.2.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl)]benzamide

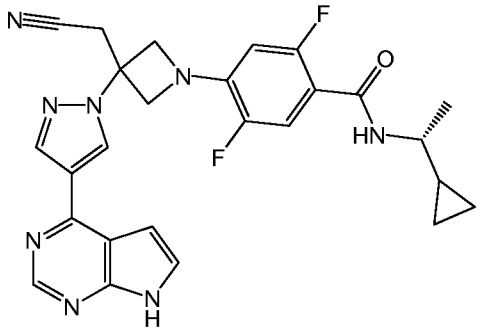
A mixture of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}benzoic acid (0.100 g, 0.189 mmol), *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.11 g, 0.29 mmol), (2*S*)-1,1,1-trifluoropropan-2-amine hydrochloride (0.042 g, 0.28 mmol) (ACS Scientific Inc., Cat. # 2-01-6) and *N,N*-diisopropylethylamine (0.13 mL, 0.76 mmol) in anhydrous 1,2-dichloroethane (3 mL) was heated at 60 °C for 15 minutes to dissolve all of the reagents and then stirred at ambient temperature overnight. The volatiles were removed *in vacuo* and the residue was partitioned between water and ethyl acetate. The organic fraction was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0 - 60%) to afford the desired intermediate (0.080g). The intermediate was dissolved in dichloromethane (3 mL) and to this was added trifluoroacetic acid (1.3 mL). After stirring at ambient temperature for 1.5 h., the volatiles were removed *in vacuo*. The residue was dissolved in methanol (1.6 mL) followed by the addition of ethylenediamine (0.2 mL, 4 mmol). After stirring at ambient temperature for 1 hour, the volatiles were removed *in vacuo* and the crude product was purified by RP-HPLC (pH = 2) to afford the desired product (0.034g) as TFA salt. LCMS $(M+H)^+$: m/z = 495.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.47 (bs, 1H), 9.00 (s, 1H), 8.77 (s, 1H), 8.50 (s, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.67 (m, 1H), 7.15 (m, 1H), 6.61 (d, *J* = 8.8 Hz, 2H), 4.82 (m, 1H), 4.59 (d, *J* = 8.5 Hz, 2H), 4.33 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 2H), 1.33 (d, *J* = 7.0 Hz, 3H).

Example 20. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(1-methylpiperidin-4-yl)ethyl]benzamide



This compound was prepared as TFA salt by using procedures analogous to those described for the synthesis of Example 19, Step 3 started from 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoic acid and 1-(1-methylpiperidin-4-yl)ethanamine (ChemBridge: Cat.# 4019769). LCMS $(M+H)^+$: m/z = 524.3.

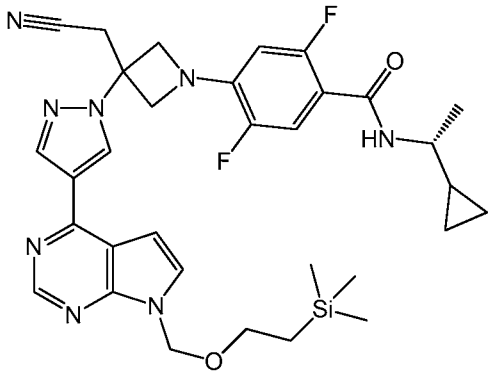
Example 21. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide



Step 1: 4-chloro-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide

Oxalyl chloride (250.0 μL, 2.954 mmol) was added to a solution of 4-chloro-2,5-difluorobenzoic acid (0.0578 g, 0.300 mmol) in dichloromethylene (3 mL), followed by 15 μL of DMF. The mixture was stirred at room temperature for 1 hour. The volatiles were removed under reduced pressure. The residue was diluted with dichloromethylene (5 mL). To the solution was added potassium carbonate (82.9 mg, 0.600 mmol) in water (1 mL), and (1R)-1-cyclopropylethanamine (41.6 μL, 0.450 mmol). The mixture was stirred at room temperature for 30 minutes, and diluted with DCM, washed with water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired product (0.075 g, 96%) which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 260.0.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide



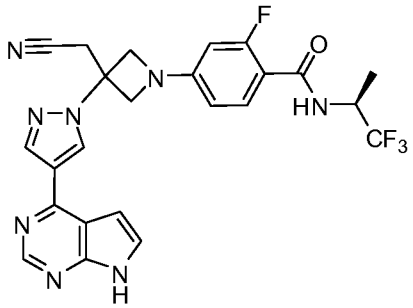
A mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (1.0 g, 2.1 mmol), 4-chloro-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide (0.54 g, 2.1 mmol), cesium carbonate (2.0 g, 6.2 mmol), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.13 g, 0.21 mmol) and palladium acetate (0.046 g, 0.21 mmol) in toluene (20 mL, 200 mmol) was stirred at 105 °C overnight. After the reaction mixture was cooled to room temperature, the solid was filtered off by celite, washed with ethyl acetate. The filtrate was concentrated. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0-60%) to afford the desired product (0.48 g, 36%). LCMS $(M+H)^+$: m/z = 633.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide

4-{3-(Cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide (0.48 g) was dissolved in a solution of trifluoroacetic acid (3 mL, 40 mmol) in methylene chloride (3 mL). The solution was stirred at room temperature for 1.5 hours. It was concentrated under reduced pressure. The residue was dissolved in methanol (5 mL). To the solution was added ethylenediamine (3 mL). The mixture was stirred at room temperature for 2 hours. After concentration the crude material was purified by flash chromatography on a silica gel column with methanol in dichloromethylene (0 – 10%) to afford the desired

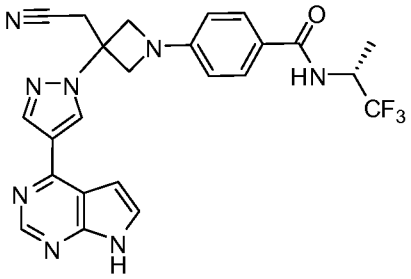
product (245 mg, 24%). LCMS $(M+H)^+$: m/z = 503.2. ^{1}H NMR (400 MHz, DMSO- d_6): δ 12.60 (s, 1H), 9.08 (s, 1H), 8.85 (s, 1H), 8.57 (s, 1H), 7.84 (dd, J = 8.0, 4.0 Hz, 1H), 7.78 (m, 1H), 7.36 (dd, J = 13.0, 7.0 Hz, 1H), 7.23 (m, 1H), 6.64 (dd, J = 13.0, 7.0 Hz, 1H), 4.70 (d, J = 8.0 Hz, 2H), 4.45 (d, J = 8.0 Hz, 2H), 3.78 (s, 2H), 3.43 (m, 1H), 1.09 (d, J = 6.5 Hz, 6H), 0.97 (m, 1H), 0.43 (m, 1H), 0.37 (m, 1H), 0.28 (m, 1H), 0.19 (m, 1H).

Example 22. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]benzamide



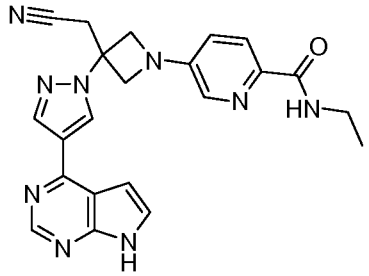
To a solution of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoic acid (25 mg, 0.046 mmol) (Example 15, Step 2) and *N,N*-diisopropylethylamine (24 μL, 0.14 mmol) in 1,2-dichloroethane (0.5 mL) was added sequentially *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (26 mg, 0.068 mmol) and (2*S*)-1,1,1-trifluoropropan-2-amine (12 mg, 0.11 mmol). After stirring at ambient temperature for 1.5 h, trifluoroacetic acid (0.5 mL) was added to the reaction mixture and stirring was continued for 1 h. The volatiles were removed in-vacuo and the residue was azeotropically washed with acetonitrile (3 x 3 mL). The resulting residue was dissolved in methanol (1 mL) and to this was added ammonium hydroxide (0.1 mL) and ethylenediamine (0.020 mL) and the reaction mixture was stirred at ambient temperature for 1 hour. The crude reaction mixture was subjected to RP-HPLC to afford the desired product. LCMS $(M+H)^+$: m/z = 513.1. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.64 (s, 1H), 9.06 (s, 1H), 8.85 (s, 1H), 8.56 (s, 1H), 8.33 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.79 (s, 1H), 7.52 (t, *J* = 8.5 Hz, 1H), 7.23 (s, 1H), 6.47 (s, 1H), 6.45-6.42 (m, 1H), 4.83–4.75 (m, 1H), 4.59 (dd, *J* = 8.9, 1.7 Hz, 2H), 4.34 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 2H), 1.31 (d, *J* = 7.1 Hz, 3H).

Example 23. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-N-[(1*R*)-2,2,2-trifluoro-1-methylethyl]benzamide bis(trifluoroacetate)



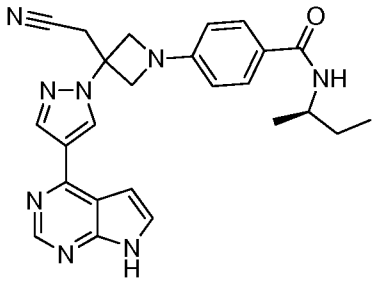
A mixture of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}benzoic acid (0.100 g, 0.189 mmol) (Example 19, Step 2), *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.11 g, 0.29 mmol), (2*R*)-1,1,1-trifluoropropan-2-amine (0.043 g, 0.38 mmol) (SynQuest, catalog # PN 3130-7-R1), and *N,N*-diisopropylethylamine (0.13 mL, 0.75 mmol) in anhydrous 1,2-dichloroethane (3.35 mL) was stirred for 30 minutes at 55 °C to dissolve the reagents. After the solution became homogeneous, the reaction was allowed to stir at ambient temperature overnight. The reaction mixture was partitioned between water and ethyl acetate. The organic fraction was washed with water, brine, dried over sodium sulfate, filtered, and concentrated *in-vacuo*. The residue was dissolved in methylene chloride (2.6 mL) and to this was added trifluoroacetic acid (1.3 mL) and the resulting solution was stirred for 1.5 h. The volatiles were removed in-vacuo and the residue was dissolved in methanol (3.2 mL) followed by the addition of ethylenediamine (0.4 mL). After stirring at ambient temperature for 1 h., the volatiles were removed *in-vacuo*. The residue was purified by RP-HPLC (pH = 2) to afford the desired product (0.080 g) as TFA salt. LCMS $(M+H)^+$: m/z = 495.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.5 (bs, 1H), 9.05 (s, 1H), 8.83 (s, 1H), 8.55 (s, 1H), 8.49 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.75 (s, 1H), 7.21 (s, 1H), 6.62 (d, J = 8.8 Hz, 2H), 4.7-4.9 (m, 1H), 4.58 (d, J = 8.7 Hz, 2H), 4.34 (d, J = 8.7 Hz, 2H), 3.77 (s, 2H), 1.33 (d, J = 7.1 Hz, 3H).

Example 24. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-ethylpyridine-2-carboxamide



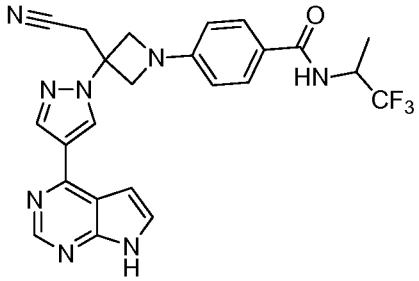
This compound was prepared by using procedures analogous to those described for the synthesis of Example 3, Step 1-3 starting from 5-bromopyridine-2-carboxylic acid, ethylamine (2.0 M in tetrahedrofuran solution) and {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride. LCMS $(M+H)^+$: m/z = 428.2.

Example 25. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-methylpropyl]benzamide bis(trifluoroacetate)



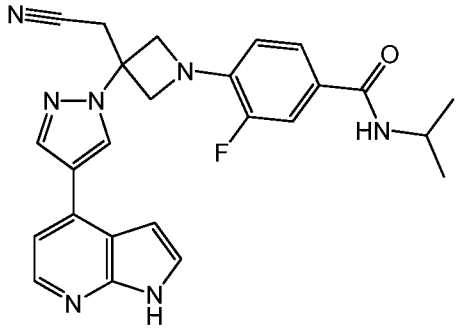
This compound was prepared as TFA salt by using procedures analogous to those described for the synthesis of Example 19, Step 3 started from 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoic acid and (2*R*)-butan-2-amine (Aldrich: Cat.#296651). LCMS $(M+H)^+$: m/z = 455.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.99 (s, 1H), 8.76 (s, 1H), 8.50 (s, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.68 (dd, *J* = 3.3, 2.5 Hz, 1H), 7.14 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.59 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 2H), 4.30 (d, *J* = 8.6 Hz, 2H), 3.89 (m, 1H), 3.75 (s, 2H), 1.58 – 1.39 (m, 2H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.84 (t, *J* = 7.4 Hz, 3H).

Example 26. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoro-1-methylethyl)benzamide



This compound was prepared as TFA salt by using procedures analogous to those described for the synthesis of Example 19, Step 3 started from 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}benzoic acid and 1-methyl-2,2,2-trifluoroethylamine hydrochloride (SynQuest Labs: Cat.#93130-7-08). LCMS $(M+H)^+$: m/z = 495.2.

Example 27. 4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide



Step 1: tert-butyl 3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

A mixture of 4-bromo-1H-pyrrolo[2,3-b]pyridine (1.1 g, 5.7 mmol), tert-butyl 3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (2.00 g, 5.15 mmol) (Example 40, Step 1), tetrakis(triphenylphosphine)palladium(0) (0.30 g, 0.26 mmol) and sodium carbonate (1.64 g, 15.4 mmol) in 1,4-dioxane (100 mL) and water (50 mL) under N_2(g) was stirred at 100 °C overnight. The reaction mixture was extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure until 5 mL of solvent was left. The resulting precipitate (0.90 g) was collected by filtration and washed with ether. The filtrate was further concentrated under reduced pressure to a volume of about 3 mL.

The precipitate formed was filtered, and washed with ether to afford additional product (0.50 g). The filtrate was concentrated under reduced pressure again. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford additional desired product (0.55 g). Total amount of product was 1.95 g (yield: 92.3%). LCMS $(M+H)^+$: m/z = 379.1.

Step 2: {3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile

Trifluoroacetic acid (7.0 mL) was added to tert-butyl 3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (0.90 g, 2.4 mmol) in methylene chloride (7.0 mL). The reaction mixture was stirred at 30 ºC for 2 h. The volatiles were removed under reduced pressure to afford the desired product (quantitative) as TFA salt which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 279.1.

Step 3: methyl 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoate

N,N-Diisopropylethylamine (1.6 mL, 9.5 mmol) was added to {3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile TFA salt (2.4 mmol) and methyl 3,4-difluorobenzoate (0.41 g, 2.4 mmol) (Aldrich, Cat.#: 594717) in N-methylpyrrolidinone (NMP) (5.0 mL). The reaction mixture was stirred at 130 °C overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford the desired product (0.34 g, 33%). LCMS $(M+H)^+$: m/z = 431.1.

Step 4: 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoic acid

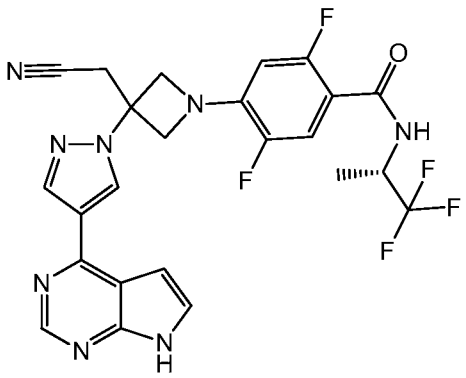
Lithium hydroxide monohydrate (83 mg, 2.0 mmol) was added to a mixture of methyl 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoate (0.34 g, 0.79 mmol) in methanol (2.0 mL), water (1.0 mL) and THF (2.0 mL). The reaction mixture was stirred at 35 °C overnight, and

adjusted to pH = 5 with 1.0 N HCl aqueous solution, and concentrated under reduced pressure to remove methanol and THF. The precipitate formed was filtered, washed with water and ether, and dried in vacuum to afford the desired product (0.17 g, 52%) which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 417.1.

Step 5: 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide

N,N-Diisopropylethylamine (63 µL, 0.36 mmol) was added to a mixture of 4-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluorobenzoic acid (50.0 mg, 0.120 mmol), and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (64 mg, 0.14 mmol) and 2-propanamine (11 mg, 0.18 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with aqueous $NaHCO_3$, and extracted with dichloromethylene (2x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 458.1.

Example 28. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide



Step 1: 4-chloro-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide

4-Chloro-2,5-difluorobenzoyl chloride (29.6 mg, 0.140 mmol) (Oakwood, Cat.#: 001628) was added to a mixture of (2S)-1,1,1-trifluoropropan-2-amine hydrochloride (20.0 mg, 0.134 mmol) (SynQuest Lab, Cat.#: 3130-7-S1) and

diisopropylethylamine (58 μL, 0.33 mmol) in dichloromethylene (4.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min., worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired product which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 288.0/290.0.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide

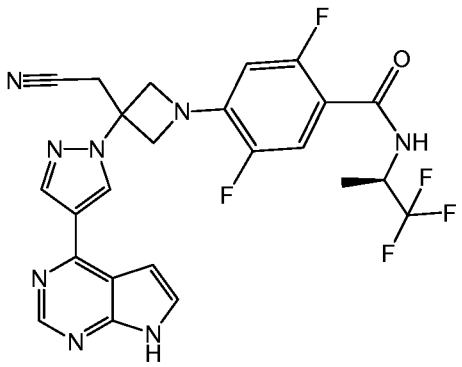
(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (8.3 mg, 0.013 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (65 mg, 0.13 mmol), 4-chloro-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide (0.14 mmol), and cesium carbonate (0.13 g, 0.40 mmol) in toluene (4.0 mL) under N_2, followed by palladium acetate (3.0 mg, 0.013 mmol). The reaction mixture was stirred at 130 °C for 5 h. After the reaction mixture was cooled to room temperature, the mixture was worked up with water, and extracted with ethyl acetate (3 x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 661.2.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide

Boron trifluoride etherate (0.051 mL, 0.40 mmol) was added to a solution of 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide in acetonitrile (1.0 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h. (LCMS $(M+H)^+$: m/z = 561.3). Then the mixture was cooled to 0 °C, water (0.13 mL) was added. After 30 min, 5.0 M ammonium hydroxide in water (0.2 mL, 1 mmol) was added slowly at 0 °C over 5 min. The reaction mixture was stirred at room temperature overnight, and

purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 531.0. ^{1}H NMR (400 MHz, DMSO-d6): δ 12.62 (br, 1H), 9.07 (s, 1H), 8.84 (s, 1H), 8.55 (s, 1H), 8.51 (dd, J = 8.8, 1.2 Hz, 1H), 7.78 (br, 1H), 7.35 (dd, J = 12.6, 6.5 Hz, 1H), 7.23 (d, J = 1.9 Hz, 1H), 6.65 (dd, J = 11.9, 7.3 Hz, 1H), 4.76 (m, 1H), 4.70 (d, J = 9.3 Hz, 2H), 4.44 (d, J = 9.2 Hz, 2H), 3.76 (s, 2H), 1.30 (d, J = 7.1 Hz, 3H).

Example 29. 4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide



Step 1: 4-chloro-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide

4-Chloro-2,5-difluorobenzoyl chloride (29.6 mg, 0.140 mmol) (Oakwood, Cat.#: 001628) was added to a solution of (2R)-1,1,1-trifluoropropan-2-amine hydrochloride (20.0 mg, 0.134 mmol) (SynQuest Lab, Cat.#: 3130-7-R1) in methylene chloride (4.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 30 min., then worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired product which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 288.0/289.9.

Step 2: 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide

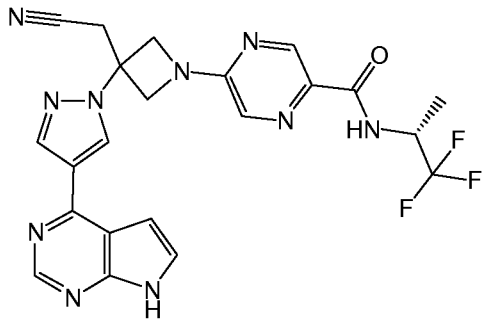
(R)-(+)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (8.3 mg, 0.013 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile

dihydrochloride (65 mg, 0.13 mmol), 4-chloro-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide (0.14 mmol), and cesium carbonate (0.13 g, 0.40 mmol) in toluene (4.0 mL) under N_2, followed by palladium acetate (3.0 mg, 0.013 mmol). The reaction mixture was stirred at 130 °C for 5 h. After the reaction mixture was cooled to room temperature, the mixture was worked up with water, and extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was directly used in the next step reaction without further purification. LCMS $(M+H)^+$: m/z = 661.3.

Step 3: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide

Boron trifluoride etherate (0.051 mL, 0.40 mmol) was added to a solution of the above intermediate in acetonitrile (1.0 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h. LCMS $(M+H)^+$: m/z = 561.2. Then the mixture was cooled to 0 °C, water (0.13 mL) was added. After 30 min., 5.0 M ammonium hydroxide in water (0.2 mL, 1 mmol) was added slowly at 0 °C in 5 min. Then the reaction mixture was stirred at room temperature overnight. The mixture was purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 531.2.

Example 30. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide



Step 1: 5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (1.3 mL, 7.5 mmol) was added to a mixture of 5-chloropyrazine-2-carboxylic acid (0.40 g, 2.5 mmol) (Matrix, Cat.#: 054028),

N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.0 g, 2.8 mmol) and (2R)-1,1,1-trifluoropropan-2-amine hydrochloride (0.38 g, 2.5 mmol) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-20%) to afford the desired product (0.64 g, 76%). LCMS $(M+H)^+$: m/z = 253.9/255.9.

Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

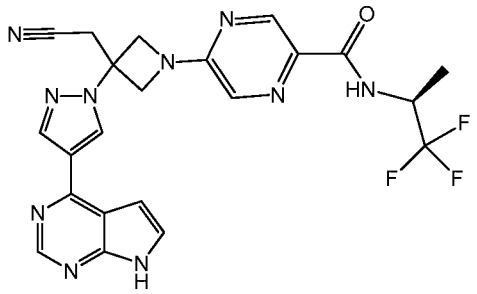
N,N-Diisopropylethylamine (0.11 mL, 0.62 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (110 mg, 0.22 mmol) and 5-chloro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide (52 mg, 0.21 mmol) in NMP (2.0 mL). The reaction mixture was stirred at 125 °C for 2 h. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0-70%) to afford the desired product. LCMS $(M+H)^+$: m/z = 627.2.

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

Boron trifluoride etherate (0.078 mL, 0.62 mmol) was added to a solution of 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide in acetonitrile (4.0 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h. [LCMS $(M+H)^+$: m/z = 527.2]. The mixture was cooled to 0 °C, water (1.6 mL) was added. After 30 min., 5.0 M ammonium hydroxide in water (0.38 mL, 1.9 mmol) was added slowly

at 0 °C over 5 min. Then the reaction mixture was stirred at room temperature overnight. The mixture was worked up with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford the desired product (60 mg, 58%). LCMS (M+H)$^+$: m/z = 497.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.73 (br, 1H), 9.13 (s, 1H), 8.87 (s, 1H), 8.83 (d, J = 9.2 Hz, 1H), 8.68 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.02 (d, J = 1.4 Hz, 1H), 7.82 (dd, J = 3.1, 2.2 Hz, 1H), 7.27 (dd, J = 3.3, 1.3 Hz, 1H), 4.83 (d, J = 9.8 Hz, 2H), 4.81 (m, 1H), 4.58 (d, J = 9.9 Hz, 2H), 3.80 (s, 2H), 1.36 (d, J = 7.1 Hz, 3H).

Example 31. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide



Step 1: 5-chloro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (1.3 mL, 7.5 mmol) was added to a mixture of 5-chloropyrazine-2-carboxylic acid (0.40 g, 2.5 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.0 g, 2.8 mmol) and (2S)-1,1,1-trifluoropropan-2-amine (0.28 g, 2.5 mmol) (Oakwood: Cat.#44272) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-15%) to afford the desired product (0.64 g, 73%). LCMS (M+H)$^+$: m/z = 253.9/255.9.

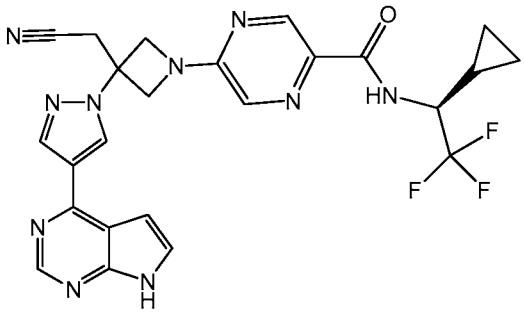
Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (0.11 mL, 0.62 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (110 mg, 0.22 mmol) and 5-chloro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide (52 mg, 0.21 mmol) in NMP (3.0 mL). The reaction mixture was stirred at 120 °C for 2 h. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0-65%) to afford the desired product (100 mg, 73%). LCMS $(M+H)^+$: m/z = 627.2.

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide

Boron trifluoride etherate (0.078 mL, 0.62 mmol) was added to a solution of 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide in acetonitrile (4.0 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h. (LCMS $(M+H)^+$: m/z = 527.2). The mixture was cooled to 0 °C, water (1.6 mL) was added. After 30 min., 5.0 M ammonium hydroxide in water (0.38 mL, 1.9 mmol) was added slowly at 0 °C in 5 min. Then the reaction mixture was stirred at room temperature overnight. The mixture was worked up with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford the desired product (52 mg, 51%). LCMS $(M+H)^+$: m/z = 497.1. ^1H NMR (400 MHz, DMSO-d_6): δ 12.60 (br, 1H), 9.09 (s, 1H), 8.84 (d, J = 8.8 Hz, 1H), 8.83 (s, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.56 (s, 1H), 8.02 (d, J = 1.4 Hz, 1H), 7.77 (br, 1H), 7.23 (br, 1H), 4.84 (d, J = 9.9 Hz, 2H), 4.80 (m, 1H), 4.57 (d, J = 9.9 Hz, 2H), 3.80 (s, 2H), 1.36 (d, J = 7.1 Hz, 3H).

Example 32. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide



Step 1: 5-chloro-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (1.3 mL, 7.5 mmol) was added to a mixture of 5-chloropyrazine-2-carboxylic acid (0.40 g, 2.5 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.0 g, 2.8 mmol) and (1S)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride (0.44 g, 2.5 mmol) (ASIBA Pharmatech, Cat.#: 70092-HCl) in methylene chloride (10 mL). The reaction mixture was stirred at room temperature overnight. The mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-20%) to afford the desired product (0.51 g, 72%). LCMS $(M+H)^+$: m/z = 280.0/282.0.

Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide

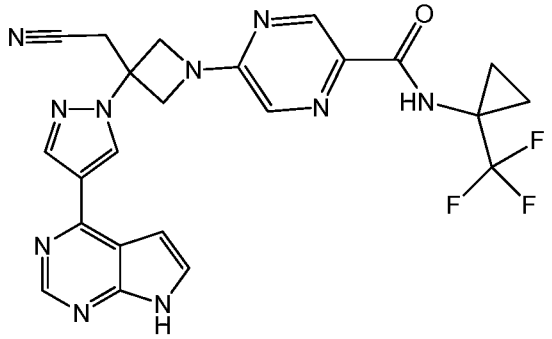
N,N-Diisopropylethylamine (0.11 mL, 0.62 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (110 mg, 0.22 mmol) and 5-chloro-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide (58 mg, 0.21 mmol) in NMP (2.0 mL). The reaction mixture was stirred at 125 °C for 2 h. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with

brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0-65%) to afford the desired product (80 mg, 59%). LCMS $(M+H)^+$: m/z = 653.2.

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide

Boron trifluoride etherate (0.078 mL, 0.62 mmol) was added to a solution of 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide in acetonitrile (4.0 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 3 h. LCMS $(M+H)^+$: m/z = 553.2. The mixture was cooled to 0 °C, then water (1.6 mL) was added. After 30 min, 5.0 M ammonium hydroxide in water (0.38 mL) was added slowly at 0 °C over 5 min. Then the reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford the desired product. LCMS $(M+H)^+$: m/z = 523.2. ^1H NMR (400 MHz, DMSO- d_6): δ 12.53 (br, 1H), 8.94 (s, 1H), 8.79 (d, J = 9.3 Hz, 1H), 8.68 (s, 1H), 8.51 (d, J = 1.4, 1H), 8.40 (s, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.63 (dd, J = 3.1, 2.3 Hz, 1H), 7.08 (dd, J = 3.3, 1.4 Hz, 1H), 4.66 (d, J = 9.9 Hz, 2H), 4.40 (d, J = 10.0 Hz, 2H), 3.82 (m, 1H), 3.63 (s, 2H), 1.22 (m, 1H), 0.48 (m, 1H), 0.38 (m, 1H), 0.30 (m, 1H), 0.02 (m, 1H).

Example 33. 5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide



Step 1: 5-chloro-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (1.3 mL, 7.5 mmol) was added to a mixture of 5-chloropyrazine-2-carboxylic acid (0.40 g, 2.5 mmol), N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.0 g, 2.8 mmol) and 1-(trifluoromethyl)cyclopropanamine (0.32 g, 2.5 mmol) (Oakwood, Cat.#: 038175) in dichloromethylene (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-20%) to afford the desired product (0.41 g, 67%). LCMS $(M+H)^+$: m/z = 266.0/267.9.

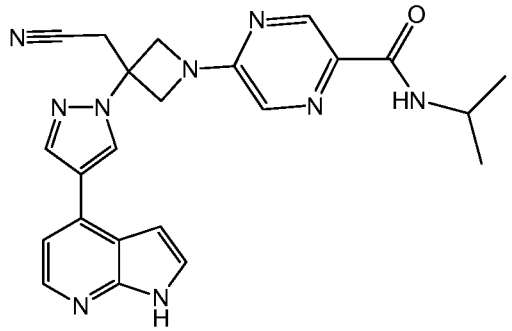
Step 2: 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide

N,N-Diisopropylethylamine (0.71 mL, 4.1 mmol) was added to a mixture of {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (0.70 g, 1.4 mmol) and 5-chloro-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide (0.36 g, 1.4 mmol) in NMP (5.0 mL). The reaction mixture was stirred at 125 °C for 2 h. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in dichloromethylene (0-80%) to afford the desired product (0.90 g). LCMS $(M+H)^+$: m/z = 639.2.

Step 3: 5-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide

Boron trifluoride etherate (0.52 mL, 4.1 mmol) was added to a solution of 5-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide (0.90 g) in acetonitrile (20 mL) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 4 h. LCMS $(M+H)^+$: m/z = 539.2. The mixture was cooled to 0 °C, water (10. mL) was added. After 30 min., 5.0 M ammonium hydroxide in water (2.5 mL) was added slowly at 0 °C in 5 min. Then the reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethylene (0-5%) to afford the desired product (0.69 g, 63%). LCMS $(M+H)^+$: m/z = 509.0. ^1H NMR (300 MHz, DMSO- d_6): δ 12.71 (br, 1H), 9.16 (s, 1H), 9.13 (s, 1H), 8.88 (s, 1H), 8.68 (d, J = 1.2 Hz, 1H), 8.60 (s, 1H), 8.02 (d, J = 1.2 Hz, 1H), 7.83 (dd, J = 3.2, 2.5 Hz, 1H), 7.28 (dd, J = 3.4, 1.4 Hz, 1H), 4.85 (d, J = 9.8 Hz, 2H), 4.59 (d, J = 10.0 Hz, 2H), 3.82 (s, 2H), 1.29 (m, 2H), 1.17 (m, 2H).

Example 34. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide



Step 1: methyl 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate

N,N-Diisopropylethylamine (1.0 mL, 6.0 mmol) was added to a mixture of {3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-

pyrazol-1-yl]azetidin-3-yl}acetonitrile dihydrochloride (0.96 g, 2.0 mmol) and methyl 5-chloropyrazine-2-carboxylate (0.34 g, 2.0 mmol) in 1,4-dioxane (15 mL). The reaction mixture was stirred at 120 °C overnight. The mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexanes (0-60%) to afford the desired product (0.13 g, 12%). LCMS $(M+H)^+$: m/z = 545.2.

Step 2: 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid

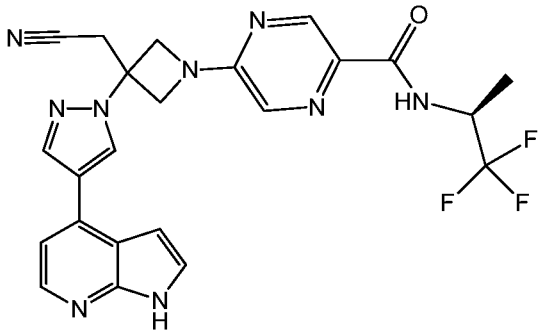
A reaction mixture of methyl 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate (0.13 g, 0.24 mmol), lithium hydroxide monohydrate (0.025 g, 0.60 mmol) in methanol (4.0 mL), THF (2.0 mL) and water (1.0 mL) was stirred at 40 °C for 3 h. The mixture was adjusted to pH = 4 with 2.0 N HCl aqueous solution, and concentrated under reduced pressure to remove MeOH and THF. The precipitate formed was filtered, washed with water and ether, and dried in vacuum to afford the desired product (0.100 g, 79%). LCMS (M+H)+ : m/z = 531.4.

Step 3: 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide

N,N-Diisopropylethylamine (19 μL, 0.11 mmol) was added to a mixture of 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid (19.4 mg, 0.0365 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (19 mg, 0.044 mmol) and 2-propanamine (3.2 mg, 0.055 mmol) in DMF (1.0 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was worked up with saturated aqueous $NaHCO_3$, and extracted with dichloromethylene (3x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was treated with methylene chloride (1.3 mL) and TFA (1.3 mL). The mixture was stirred at room temperature for 1.5 h., and concentrated under reduced pressure. The residue was dissolved in methanol (1.3 mL), and treated with

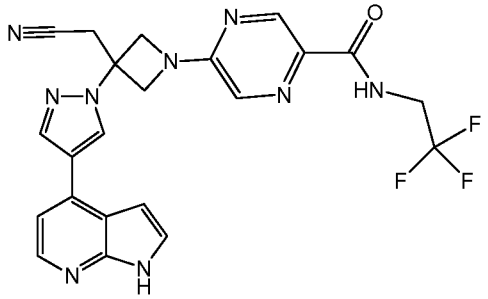
ethylenediamine (0.086 mL, 1.3 mmol). The resulting mixture was stirred at room temperature for 2 h, and then purified by RP-HPLC (pH = 10) to afford the desired product. LCMS $(M+H)^+$: m/z = 442.1. ^{1}H NMR (400 MHz, DMSO- d_6): δ 12.19 (br, 1H), 8.99 (s, 1H), 8.66 (d, J = 1.4 Hz, 1H), 8.47 (s, 1H), 8.32 (d, J = 5.7 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 1.4 Hz, 1H), 7.67 (dd, J = 3.2, 2.7 Hz, 1H), 7.54 (d, J = 5.5 Hz, 1H), 7.09 (dd, J = 3.5, 2.7 Hz), 4.82 (d, J = 10.0 Hz, 2H), 4.56 (d, J = 10.0 Hz, 2H), 4.10 (m, 1H), 3.79 (s, 2H), 1.17 (d, J = 6.4 Hz, 6H).

Example 35. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide



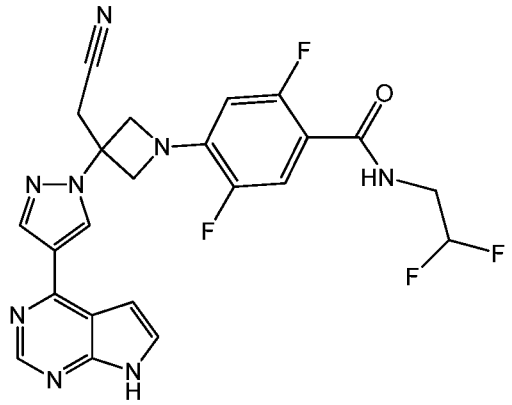
This compound was prepared by using procedures analogous to those described for the synthesis of Example 34, Step 3 starting from 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid and (2S)-1,1,1-trifluoropropan-2-amine hydrochloride. LCMS $(M+H)^+$: m/z = 496.1. ^{1}H NMR (400 MHz, DMSO- d_6) δ 12.23 (br, 1H), 8.99 (s, 1H), 8.83 (d, J = 9.3 Hz, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.47 (s, 1H), 8.32 (d, J = 5.6 Hz, 1H), 8.02 (d, J = 1.4 Hz, 1H), 7.67 (dd, J = 3.3, 2.6 Hz, 1H), 7.55 (d, J = 5.5 Hz, 1H), 7.09 (dd, J = 3.4, 1.7 Hz), 4.83 (d, J = 10.0 Hz, 2H), 4.80 (m, 1H), 4.57 (d, J = 9.6 Hz, 2H), 3.78 (s, 2H), 1.36 (d, J = 7.2 Hz, 3H).

Example 36. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide



This compound was prepared by using procedures analogous to those described for the synthesis of Example 34, Step 3 starting from 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid and 2,2,2-trifluoroethanamine. LCMS $(M+H)^+$: m/z = 482.1.

Example 37. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-(2,2-difluoroethyl)-2,5-difluorobenzamide



Step 1: 4-chloro-N-(2,2-difluoroethyl)-2,5-difluorobenzamide

A solution of 4-chloro-2,5-difluorobenzoic acid (1.28 g, 6.64 mmol), *N,N*-diisopropylethylamine (3.5 mL, 20 mmol), and *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (3.07 g, 8.07 mmol) in 1,2-dichloroethane (20 mL) was stirred for 10 min. at room temperature prior to the addition of a solution of 2,2-difluoroethanamine (538 mg, 6.64 mmol) in dichloroethane (2 mL). The resulting solution was stirred for 1 h. at room temperature. LCMS data indicated that the major reaction component was the desired product. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-10%) to afford the desired product. LCMS $(M+H)^+$: m/z = 256.0.

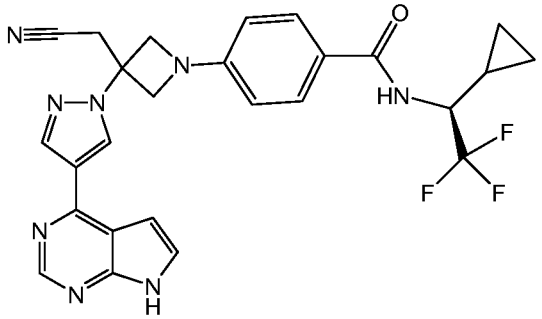
Step 2: 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2-difluoroethyl)-2,5-difluorobenzamide

A solution of 4-chloro-*N*-(2,2-difluoroethyl)-2,5-difluorobenzamide (0.907 g, 3.55 mmol), {3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl}acetonitrile HCl salt (1.57 g, 3.52 mmol), palladium acetate (55 mg, 0.24 mmol), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (285 mg, 0.493 mmol) and cesium carbonate (2.16 g, 6.63 mmol) in toluene (25 mL) was de-gassed and purged with N_2 (g) several times prior to heating to 105 °C and stirring for 3 d. LCMS data indicated that ~50% of the starting material was converted to the desired product. In an effort to drive the reaction to completion a second aliquot of 4-chloro-*N*-(2,2-difluoroethyl)-2,5-difluorobenzamide (353 mg), palladium acetate (58 mg), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (274 mg), and cesium carbonate (550 mg) was added and stirring was continued overnight at 105 °C. LCMS data indicated that there was no significant improvement. The crude reaction mixture was filtered through a pad of celite and the inorganics were washed thoroughly with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-15%) to afford the desired product (0.789 g).

The above pure product was dissolved in dichloromethane (10 mL) and treated with trifluoroacetic acid (10 mL). The mixture was stirred at ambient temperature for 2.5 h. The volatiles were removed under reduced pressure and the residue was azeotropically washed with acetonitrile (3 x 10 mL). The resulting residue was dissolved in methanol (20 mL) and treated with NH_4OH aqueous solution (2 mL). The reaction mixture was stirred at ambient temperature for 2 h. The crude reaction mixture was concentrated in-vacuo and subjected to flash chromatography on a silica gel column with methanol in dichloromethane (0-15%) to afford the desired product (229 mg). The product was dissolved in acetonitrile (15 mL) and cooled to 0 °C prior to the addition of trifluoroacetic acid (0.2 mL). The reaction mixture was allowed to warm to ambient temperature while stirring for 30 min. Water (10 mL) was added and the solution was frozen and subjected to lyophilization to afford the desired product as the corresponding trifluoroacetic acid salt. LCMS $(M+H)^+$: m/z = 499.4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.73 (s, 1H), 9.11 (s, 1H), 8.88 (s, 1H), 8.58 (s, 1H), 8.26

(q, *J* = 5.7 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.43 (dd, *J* = 12.7, 6.5 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 6.65 (dd, *J* = 12.3, 7.3 Hz, 1H), 6.09 (tt, *J* = 56.1, 4.1 Hz, 1H), 4.72 (d, *J* = 8.8 Hz, 2H), 4.47 (d, *J* = 7.8 Hz, 2H), 3.76 (s, 2H), 3.64 (tt, *J* = 15.4, 4.4 Hz, 2H).

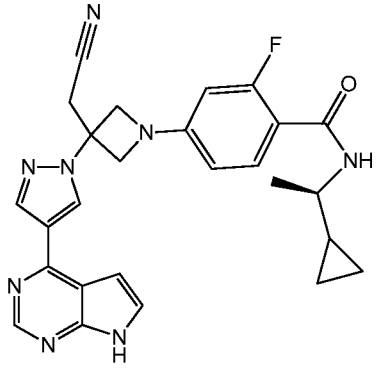
Example 38. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-[(1*S*)-1-cyclopropyl-2,2,2-trifluoroethyl]benzamide



To an oven dried vial containing (1*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine HCl salt (130 mg, 0.74 mmol) (ASIBA Pharmatech, Cat.#: 70092-HCl) and equipped with a magnetic stirring bar was placed anhydrous 1,2-dichloroethane (0.5 mL) followed by *N,N*-diisopropylethylamine (140 µL, 0.83 mmol). The reaction vial was purged with N_2 (g) and sealed prior to the addition of 2.0 M trimethylaluminum in toluene (180 µL, 0.37 mmol). After stirring at room temperature for 20 min., a solution of methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}benzoate (100. mg, 0.184 mmol) (Example 19, Step 1) in 1,2-dichloroethane (1.0 mL) was added and the reaction mixture was heated at 65 °C and stirred for 16 h. LCMS data indicated that the reaction was ~50% complete. A second aliquot of a pre-stirred solution of (1*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine HCl salt (130 mg), *N,N*-diisopropylethylamine (140 µL), and 2.0 M trimethylaluminum in toluene (180 µL) in 1,2-dichloroethane (0.5 mL) was added and stirring was continued for 4 h. LC/MS data indicated that the reaction was complete. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (4 mL) and DOWEX 50WX8-400 ion-exchange resin was carefully added to the reaction mixture. After stirring at room temperature for 30 min, the inorganics were filtered off and thoroughly washed with dichloromethane. The crude reaction mixture was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-10%) to afford the desired product (90 mg, 75% yield). The pure product was dissolved in

dichloromethane (2 mL) and trifluoroacetic acid (2 mL) and was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the residue was azeotropically washed with acetonitrile (3 x 3 mL). The resulting residue was dissolved in methanol (3 mL), and NH_4OH aqueous solution (200 μL) and ethylenediamine (50 μL) were added and the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was subjected to RP-HPLC (pH = 2) to afford the desired product as the corresponding trifluoroacetic acid salt as a white solid. LCMS $(M+H)^+$: m/z = 521.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.48 (s, 1H), 9.03 (s, 1H), 8.80 (s, 1H), 8.66 (d, J = 8.9 Hz, 1H), 8.53 (s, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 7.18 (s, 1H), 6.62 (d, J = 8.7 Hz, 2H), 4.58 (d, J = 8.7 Hz, 2H), 4.33 (d, J = 8.7 Hz, 2H), 4.08 (dt, J = 17.3, 8.6 Hz, 1H), 3.76 (s, 2H), 1.30 – 1.19 (m, 1H), 0.68 (dt, J = 12.4, 5.6 Hz, 1H), 0.51 (q, J = 7.8, 6.8 Hz, 2H), 0.29 – 0.23 (m, 1H).

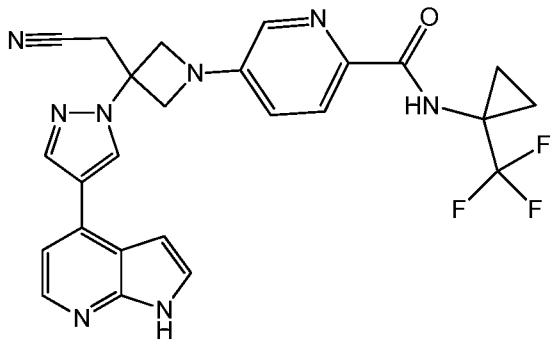
Example 39. 4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-[(1*R*)-1-cyclopropylethyl]-2-fluorobenzamide



To a sealed vial that was purged with N_2 (g) and contained a solution of (1*R*)-1-cyclopropylethanamine (150 μL, 1.62 mmol) (Alfa Aesar H26902 lot 10151885, CAS 6240-96-9, 98% ee) in 1,2-dichloroethane (2 mL) was added 2.0 M trimethylaluminum in toluene (0.800 mL, 1.60 mmol) via syringe and the resulting solution was stirred at room temperature for 30 min. A solution of methyl 4-{3-(cyanomethyl)-3-[4-(7-{[2-(trimethylsilyl)ethoxy]methyl}-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-2-fluorobenzoate (300. mg, 0.534 mmol) (Example 15, Step 1) in 1,2-dichloroethane (3 mL) was added drop-wise via syringe. The solution was heated to 70 °C and stirred for 16 h. LCMS data indicated that ~60% of the starting material was converted to the desired product. In an effort to drive the reaction to completion a pre-stirred solution of (1*R*)-1-

cyclopropylethanamine (150 μL) and 2.0 M trimethylaluminum in toluene (800 μL) in 1,2-dichloroethane (2 mL) was added via syringe to the reaction mixture at room temperature. The reaction mixture was then heated to 70 °C and stirred for 16 h. LCMS data indicated that the majority of the starting material was converted to the desired product. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (5 mL) and DOWEX 50WX8-400 ion-exchange resin was carefully added and the reaction mixture was stirred for 30 min. The inorganics were filtered off and thoroughly washed with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on a silica gel column with methanol in dichloromethane (0-5%) to afford the desired product (100 mg). The product was dissolved in dichloromethane (4 mL) and TFA (4 mL) and was stirred at room temperature for 1.5 h. The volatiles were removed under reduced pressure and the residue was azeotropically washed with acetonitrile (3 x 3 mL). The resulting residue was dissolved in methanol (4 mL) and NH_4OH aqueous solution (1 mL) was added and the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was concentrated under reduced pressure and subjected to flash chromatography on a silica gel column with methanol in dichloromethane (0-10%) to afford the desired product. The product was dissolved in acetonitrile (15 mL) and cooled to 0 °C prior to the addition of trifluoroacetic acid (0.08 mL). The reaction mixture was allowed to warm to ambient temperature while stirring for 30 min. Water (10 mL) was added and the solution was frozen and subjected to lyophilization to afford the desired product as the corresponding trifluoroacetic acid salt as a white solid. LCMS $(M+H)^+$: m/z = 485.5. ^1H NMR (500 MHz, CD_3OD): δ 9.02 (s, 1H), 8.85 (s, 1H), 8.53 (s, 1H), 7.78 (d, J = 3.7 Hz, 1H), 7.67 (t, J = 8.5 Hz, 1H), 7.26 (d, J = 3.7 Hz, 1H), 6.47 (dd, J = 8.6, 2.0 Hz, 1H), 6.40 (dd, J = 13.5, 1.9 Hz, 1H), 4.61 (d, J = 8.7 Hz, 2H), 4.44 (d, J = 8.7 Hz, 2H), 3.67 (s, 2H), 3.51 (p, J = 6.8 Hz, 1H), 1.29 (d, J = 6.7 Hz, 3H), 0.98 (ddt, J = 13.2, 8.3, 4.2 Hz, 1H), 0.54 (td, J = 8.4, 4.5 Hz, 1H), 0.47 (tt, J = 8.9, 5.3 Hz, 1H), 0.37 (dq, J = 9.8, 5.0 Hz, 1H), 0.26 (dq, J = 9.5, 4.9 Hz, 1H).

Example 40. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide



Step 1: tert-butyl 3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.0 g, 10. mmol), tert-butyl 3-(cyanomethylene)azetidine-1-carboxylate (2.0 g, 10. mmol) (Example 2, Step 2) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1 mL, 7 mmol) in acetonitrile (3 mL) was stirred at 50 °C overnight. After cooling the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0 - 50%) to afford the desired product (quantitative). LCMS $(M+Na)^+$: m/z = 411.2; $(M-C4H9)^+$: m/z = 333.1.

Step 2: tert-butyl 3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate

A mixture of 4-bromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridine (1.0 g, 3.0 mmol), tert-butyl 3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (1.2 g, 3.0 mmol), tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.2 mmol) and cesium carbonate (3.0 g, 9.2 mmol) in 1,4-dioxane (6 mL) and water (0.9 mL) was degassed and sealed. It was stirred at 90 °C for 2 h. After cooling it was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with ethyl acetate in hexane (0 - 50%) to afford the desired product (1.6 g). LCMS $(M+H)^+$: m/z = 509.3.

Step 3: {3-[4-(1-{[2-(Trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile

To a solution of tert-butyl 3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-

yl]azetidine-1-carboxylate (1.6 g) in methylene chloride (10 mL) was added a solution of 4.0 M of hydrogen chloride in dioxane (20 mL). The mixture was stirred at room temperature overnight. Then it was concentrated under reduced pressure to afford the desired compound as HCl salt (1.5 g). LCMS $(M+H)^+$: m/z = 409.2.

Step 4: 5-bromo-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

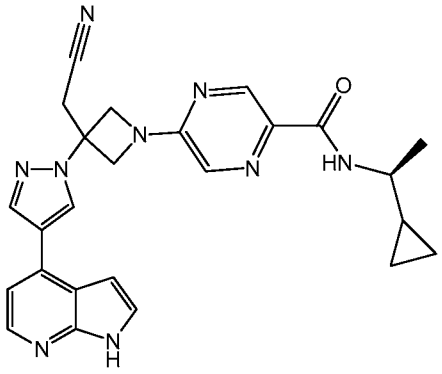
A mixture of 5-bromopyridine-2-carboxylic acid (150 mg, 0.74 mmol) , 1-(trifluoromethyl)cyclopropanamine (93 mg, 0.74 mmol) (Oakwood, Cat.#: 038175), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (345 mg, 0.780 mmol) and triethylamine (310 μL, 2.2 mmol) in methylene chloride (1 mL) was stirred at room temperature for 3 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in dichloromethylene (0 - 5%) to afford the desired product (124 mg). LCMS $(M+H)^+$: m/z = 309.0.

Step 5: 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide

A mixture of {3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile HCl salt (40 mg, 0.08 mmol), 5-bromo-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide 26 mg, 0.083 mmol), cesium carbonate (81 mg, 0.25 mmol), (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5.2 mg, 0.0083 mmol) and palladium acetate (1.9 mg, 0.0083 mmol) in toluene (1 mL) was stirred at 105 °C overnight. After the reaction mixture was cooled to room temperature, the solid was separated, and washed with ethyl acetate twice. The combined organic solution was concentrated under reduced pressure. The residue was dissolved in a solution of trifluoroacetic acid (1 mL) in methylene chloride (1:1, 1 mL). After stirred at room temperature for 1.5 h., the mixture was concentrated under reduced pressure. The residue was dissolved in methanol (1 mL). To the solution was added ethylenediamine (0.6 mL). The mixture was stirred at room temperature for 2 h. The product was purified with RP-HPLC (pH = 2) to afford the desired product (3.4 mg) as TFA salt. LCMS $(M+H)^+$: m/z = 507.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.98 (s, 1H), 9.04 (s, 1H), 8.89 (s, 1H), 8.39 (s, 1H), 8.26 (d, J = 5.3 Hz, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.88 (d, J = 8.6 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.45 (d, J = 5.3 Hz, 1H), 7.09 (dd, J = 8.5, 2.7 Hz, 1H), 6.99 (dd, J =

3.2, 1.4 Hz, 1H), 4.68 (d, *J* = 8.9 Hz, 2H), 4.42 (d, *J* = 8.9 Hz, 2H), 3.75 (s, 2H), 1.32 – 1.23 (m, 2H), 1.22 – 1.12 (m, 2H).

Example 41. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide



Step 1: 5-Chloro-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide

A mixture of 5-chloropyrazine-2-carboxylic acid (0.5 g, 3 mmol), (1S)-1-cyclopropylethanamine (0.30 g, 3.5 mmol) , N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (1.8 g, 4.7 mmol) and N,N-diisopropylethylamine (1.6 mL, 9.5 mmol) in methylene chloride (5 mL) was stirred at room temperature overnight (22 h.). The mixture was concentrated under reduced pressure. The residue was was purified by flash chromatography on a silica gel column with methanol in dichloromethylene (0 - 5%) to afford the desired product (0.54 g). LCMS $(M+H)^+$: m/z = 226.1.

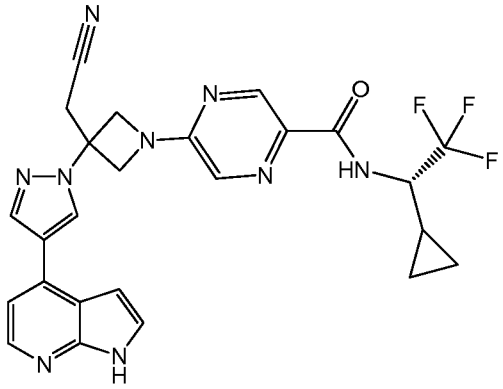
Step 2: 5-{3-(cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide

A mixture of {3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile HCl salt (200 mg, 0.4 mmol) (Example 40, Step 3), 5-chloro-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide (100 mg, 0.46 mmol) in N,N-diisopropylethylamine (0.7 mL, 4 mmol) in a sealed vial was stirred at 120 °C for 1.5 h. After cooling it was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford the desired product (0.23 g).

Step3: 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide

5-{3-(Cyanomethyl)-3-[4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide (0.23 g) was dissolved in a solution of trifluoroacetic acid (2 mL) and methylene chloride (2 mL). The mixture was stirred at room temperature for 2 h, and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford an intermediate which was dissolved in methanol (3.0 mL). To the solution was added ethylenediamine (1.0 mL). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford the desired product (0.13 g). LCMS $(M+H)^+$: m/z = 468.5. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.13 (s, 1H), 8.96 (s, 1H), 8.65 (d, J = 1.3 Hz, 1H), 8.44 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.00 (d, J = 1.3 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.52 (d, J = 5.5 Hz, 1H), 7.09 – 7.04 (m, 1H), 4.82 (d, J = 9.7 Hz, 2H), 4.56 (d, J = 9.7 Hz, 2H), 3.77 (s, 2H), 3.50 – 3.28 (m, 1H), 1.22 (d, J = 6.7 Hz, 3H), 1.15 – 0.98 (m, 1H), 0.49 – 0.39 (m, 1H), 0.39 – 0.30 (m, 1H), 0.29 – 0.22 (m, 1H), 0.22 – 0.15 (m, 1H).

Example 42. 5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide



Step 1: {3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile

A mixture of tert-butyl 3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidine-1-carboxylate (1.5 g, 3.9 mmol) (Example 40, Step 1) in methylene chloride (15 mL) and 4.0 M hydrogen chloride in dioxane (3.9 mL) was stirred at room temperature over weekend. The mixture was treated with triethylamine (1 mL), and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford the desired product (0.95 g, 85%). LCMS $(M+H)^+$: m/z = 289.2.

Step 2: Methyl 5-{3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate

A mixture of {3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile HCl salt (400. mg, 1.23 mmol), methyl 5-chloropyrazine-2-carboxylate (223 mg, 1.29 mmol), cesium carbonate (800 mg, 2.5 mmol), palladium acetate (28 mg, 0.12 mmol) and (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (150 mg, 0.25 mmol) in toluene (5 mL) was stirred at 100 °C for 3 h. After the reaction mixture was cooled to room temperature, the solid was separated, and washed with ethyl acetate twice. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford the desired product (0.28 g). LCMS $(M+H)^+$: m/z = 425.2.

Step 3: Methyl 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate

A mixture of methyl 5-{3-(cyanomethyl)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate (0.28 g, 0.66 mmol), 4-bromo-1H-pyrrolo[2,3-b]pyridine (0.14 g, 0.72 mmol), tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol) and sodium bicarbonate (0.28 g, 3.3 mmol) in a solution of water (0.5 mL) and 1,4-dioxane (1 mL) was degassed for a while and sealed. The mixture was stirred at 85 °C for 3 h. After cooling the mixture was diluted with ethyl acetate. The organic solution was washed with water and brine, dried over Na_2SO_4. After filtration the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column with methanol in methylene chloride (0 - 5%) to afford the desired

product (0.15 g). LCMS $(M+H)^+$: m/z = 415.2.

Step 4: 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid

A mixture of methyl 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylate (0.15 g, 0.36 mmol) and lithium hydroxide monohydrate (46 mg, 1.1 mmol) in methanol (3 mL) and water (1 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure to afford the desired product (quantitative) which was directly used in the next step reaction without further purification.

Step 5: 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide

A mixture of 5-{3-(cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}pyrazine-2-carboxylic acid (10 mg, 0.02 mmol), (1S)-1-cyclopropyl-2,2,2-trifluoroethanamine HCl salt (6.6 mg, 0.037 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (12 mg, 0.027 mmol) and triethylamine (16 μL, 0.11 mmol) in N,N-dimethylformamide (0.3 mL) was stirred at room temperature for 3 h. It was diluted with methanol, purified by RP-HPLC (pH =2) to afford the desired product (2.9 mg) as TFA salt. LCMS $(M+H)^+$: m/z = 522.4. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.01 (s, 1H), 8.92 (s, 1H), 8.90 (d, J = 9.4 Hz, 1H), 8.69 (d, J = 1.1 Hz, 1H), 8.41 (s, 1H), 8.27 (d, J = 5.3 Hz, 1H), 8.04 (d, J = 1.0 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.46 (d, J = 5.3 Hz, 1H), 7.01 (s, 1H), 4.84 (d, J = 9.8 Hz, 2H), 4.58 (d, J = 9.8 Hz, 2H), 4.10 – 3.97 (m, 1H), 3.78 (s, 2H), 1.46 – 1.33 (m, 1H), 0.73 – 0.61 (m, 1H), 0.61 – 0.53 (m, 1H), 0.53 – 0.44 (m, 1H), 0.27– 0.17 (m, 1H).

Example A: *In vitro* JAK Kinase Assay

Compounds herein were tested for inhibitory activity of JAK targets according to the following *in vitro* assay described in Park *et al.*, *Analytical Biochemistry* **1999**, *269*, 94-104. The catalytic domains of human JAK1 (a.a. 837-1142), JAK2 (a.a. 828-1132) and JAK3 (a.a. 781-1124) with an N-terminal His tag were expressed using baculovirus in insect cells and purified. The catalytic activity of JAK1, JAK2 or JAK3 was assayed by measuring the phosphorylation of a biotinylated peptide. The

phosphorylated peptide was detected by homogenous time resolved fluorescence (HTRF). IC_{50}s of compounds were measured for each kinase in the 40 microL reactions that contain the enzyme, ATP and 500 nM peptide in 50 mM Tris (pH 7.8) buffer with 100 mM NaCl, 5 mM DTT, and 0.1 mg/mL (0.01%) BSA. For the 1 mM IC_{50} measurements, ATP concentration in the reactions was 1 mM. Reactions were carried out at room temperature for 1 hour and then stopped with 20 μL 45 mM EDTA, 300 nM SA-APC, 6 nM Eu-Py20 in assay buffer (Perkin Elmer, Boston, MA). Binding to the Europium labeled antibody took place for 40 minutes and HTRF signal was measured on a Fusion plate reader (Perkin Elmer, Boston, MA). See Table 1 for data related to compounds of the examples.

Table 1. IC_{50} data for JAK enzyme assay (at 1 mM ATP)

Example No.	JAK1 IC_{50} (nM)*	JAK2 IC_{50} (nM)*	JAK2/ JAK1**
1	+	++	A
2	+	+	A
3	+	+	A
4	+	+	A
5	+	+	A
6	+	+	A
7	+	+	A
8	+	+	A
9	+	+	A
10	+	+	A
11	+	+	A
12	+	+	A
13	+	++	A
14	+	++	A
15	+	++	A
16	+	+	A
17	+	+	A
18	+	++	A
19	+	++	A
20	+	++	A
21	+	+	A
22	+	++	A
23	+	++	A
24	+	+	A
25	+	+	A
26	+	++	A
27	+	+	A
28	+	+	A

29	+	+	A
30	+	++	A
31	+	+	A
32	+	+	A
33	+	++	A
34	+	++	A
35	+	++	A
36	+	++	A
37	+	+	A
38	+	++	A
39	+	++	A
40	+	++	A
41	+	++	A
42	+	++	A

*10 nM or less (+); >10 nM to 40 nM (++)
**A means greater than or equal to 10

Example B: Cellular Assays

Cancer cell lines dependent on cytokines and hence JAK/STAT signal transduction, for growth, can be plated at 6000 cells per well (96 well plate format) in RPMI 1640, 10% FBS, and 1 nG/mL of appropriate cytokine. Compounds can be added to the cells in DMSO/media (final concentration 0.2% DMSO) and incubated for 72 hours at 37 °C, 5% CO_2. The effect of compound on cell viability is assessed using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) followed by TopCount (Perkin Elmer, Boston, MA) quantitation. Potential off-target effects of compounds are measured in parallel using a non-JAK driven cell line with the same assay readout. All experiments are typically performed in duplicate.

The above cell lines can also be used to examine the effects of compounds on phosphorylation of JAK kinases or potential downstream substrates such as STAT proteins, Akt, Shp2, or Erk. These experiments can be performed following an overnight cytokine starvation, followed by a brief preincubation with compound (2 hours or less) and cytokine stimulation of approximately 1 hour or less. Proteins are then extracted from cells and analyzed by techniques familiar to those schooled in the art including Western blotting or ELISAs using antibodies that can differentiate between phosphorylated and total protein. These experiments can utilize normal or cancer cells to investigate the activity of compounds on tumor cell survival biology or on mediators of inflammatory disease. For example, with regards to the latter, cytokines such as IL-6, IL-12, IL-23, or IFN can be used to stimulate JAK activation

resulting in phosphorylation of STAT protein(s) and potentially in transcriptional profiles (assessed by array or qPCR technology) or production and/or secretion of proteins, such as IL-17. The ability of compounds to inhibit these cytokine mediated effects can be measured using techniques common to those schooled in the art.

Compounds herein can also be tested in cellular models designed to evaluate their potency and activity against mutant JAKs, for example, the JAK2V617F mutation found in myeloid proliferative disorders. These experiments often utilize cytokine dependent cells of hematological lineage (*e.g.* BaF/3) into which the wild-type or mutant JAK kinases are ectopically expressed (James, C., *et al. Nature* 434:1144-1148; Staerk, J., *et al.* JBC 280:41893-41899). Endpoints include the effects of compounds on cell survival, proliferation, and phosphorylated JAK, STAT, Akt, or Erk proteins.

Certain compounds herein can be evaluated for their activity inhibiting T-cell proliferation. Such as assay can be considered a second cytokine (*i.e.* JAK) driven proliferation assay and also a simplistic assay of immune suppression or inhibition of immune activation. The following is a brief outline of how such experiments can be performed. Peripheral blood mononuclear cells (PBMCs) are prepared from human whole blood samples using Ficoll Hypaque separation method and T-cells (fraction 2000) can be obtained from PBMCs by elutriation. Freshly isolated human T-cells can be maintained in culture medium (RPMI 1640 supplemented with10% fetal bovine serum, 100 U/ml penicillin, 100 μg/ml streptomycin) at a density of 2 x 10^6 cells/ml at 37 °C for up to 2 days. For IL-2 stimulated cell proliferation analysis, T-cells are first treated with Phytohemagglutinin (PHA) at a final concentration of 10 μg/mL for 72 hours. After washing once with PBS, 6000 cells/well are plated in 96-well plates and treated with compounds at different concentrations in the culture medium in the presence of 100 U/mL human IL-2 (ProSpec-Tany TechnoGene; Rehovot, Israel). The plates are incubated at 37 °C for 72h and the proliferation index is assessed using CellTiter-Glo Luminescent reagents following the manufactory suggested protocol (Promega; Madison, WI).

Example C: *In vivo* anti-tumor efficacy

Compounds herein can be evaluated in human tumor xenograft models in immune compromised mice. For example, a tumorigenic variant of the INA-6

plasmacytoma cell line can be used to inoculate SCID mice subcutaneously (Burger, R., *et al. Hematol* J. 2:42-53, 2001). Tumor bearing animals can then be randomized into drug or vehicle treatment groups and different doses of compounds can be administered by any number of the usual routes including oral, i.p., or continuous infusion using implantable pumps. Tumor growth is followed over time using calipers. Further, tumor samples can be harvested at any time after the initiation of treatment for analysis as described above (Example B) to evaluate compound effects on JAK activity and downstream signaling pathways. In addition, selectivity of the compound(s) can be assessed using xenograft tumor models that are driven by other know kinases (*e.g.* Bcr-Abl) such as the K562 tumor model.

Example D: Murine Skin Contact Delayed Hypersensitivity Response Test

Compounds herein can also be tested for their efficacies (of inhibiting JAK targets) in the T-cell driven murine delayed hypersensitivity test model. The murine skin contact delayed-type hypersensitivity (DTH) response is considered to be a valid model of clinical contact dermatitis, and other T-lymphocyte mediated immune disorders of the skin, such as psoriasis (*Immunol Today*. 1998 Jan;19(1):37-44). Murine DTH shares multiple characteristics with psoriasis, including the immune infiltrate, the accompanying increase in inflammatory cytokines, and keratinocyte hyperproliferation. Furthermore, many classes of agents that are efficacious in treating psoriasis in the clinic are also effective inhibitors of the DTH response in mice (Agents Actions. 1993 Jan;38(1-2):116-21).

On Day 0 and 1, Balb/c mice are sensitized with a topical application, to their shaved abdomen with the antigen 2,4,dinitro-fluorobenzene (DNFB). On day 5, ears are measured for thickness using an engineer's micrometer. This measurement is recorded and used as a baseline. Both of the animals' ears are then challenged by a topical application of DNFB in a total of 20 μL (10 μL on the internal pinna and 10 μL on the external pinna) at a concentration of 0.2%. Twenty-four to seventy-two hours after the challenge, ears are measured again. Treatment with the test compounds is given throughout the sensitization and challenge phases (day -1 to day 7) or prior to and throughout the challenge phase (usually afternoon of day 4 to day 7). Treatment of the test compounds (in different concentration) is administered either systemically or topically (topical application of the treatment to the ears). Efficacies of the test compounds are indicated by a reduction in ear swelling

comparing to the situation without the treatment. Compounds causing a reduction of 20% or more were considered efficacious. In some experiments, the mice are challenged but not sensitized (negative control).

The inhibitive effect (inhibiting activation of the JAK-STAT pathways) of the test compounds can be confirmed by immunohistochemical analysis. Activation of the JAK-STAT pathway(s) results in the formation and translocation of functional transcription factors. Further, the influx of immune cells and the increased proliferation of keratinocytes should also provide unique expression profile changes in the ear that can be investigated and quantified. Formalin fixed and paraffin embedded ear sections (harvested after the challenge phase in the DTH model) are subjected to immunohistochemical analysis using an antibody that specifically interacts with phosphorylated STAT3 (clone 58E12, Cell Signaling Technologies). The mouse ears are treated with test compounds, vehicle, or dexamethasone (a clinically efficacious treatment for psoriasis), or without any treatment, in the DTH model for comparisons. Test compounds and the dexamethasone can produce similar transcriptional changes both qualitatively and quantitatively, and both the test compounds and dexamethasone can reduce the number of infiltrating cells. Both systemically and topical administration of the test compounds can produce inhibitive effects, *i.e.*, reduction in the number of infiltrating cells and inhibition of the transcriptional changes.

Example E: *In vivo* anti-inflammatory activity

Compounds herein can be evaluated in rodent or non-rodent models designed to replicate a single or complex inflammation response. For instance, rodent models of arthritis can be used to evaluate the therapeutic potential of compounds dosed preventatively or therapeutically. These models include but are not limited to mouse or rat collagen-induced arthritis, rat adjuvant-induced arthritis, and collagen antibody-induced arthritis. Autoimmune diseases including, but not limited to, multiple sclerosis, type I-diabetes mellitus, uveoretinitis, thyroditis, myasthenia gravis, immunoglobulin nephropathies, myocarditis, airway sensitization (asthma), lupus, or colitis may also be used to evaluate the therapeutic potential of compounds herein. These models are well established in the research community and are familiar to those schooled in the art (Current Protocols in Immunology, Vol 3., Coligan, J.E. *et al*,

Wiley Press.; *Methods in Molecular Biology*: Vol. 225, Inflammation Protocols., Winyard, P.G. and Willoughby, D.A., Humana Press, 2003.).

Example F: Animal Models for the Treatment of Dry Eye, Uveitis, and Conjunctivitis

Agents may be evaluated in one or more preclinical models of dry eye known to those schooled in the art including, but not limited to, the rabbit concanavalin A (ConA) lacrimal gland model, the scopolamine mouse model (subcutaneous or transdermal), the Botulinumn mouse lacrimal gland model, or any of a number of spontaneous rodent auto-immune models that result in ocular gland dysfunction (e.g. NOD-SCID, MRL/lpr, or NZB/NZW) (Barabino et al., Experimental Eye Research 2004, 79, 613-621 and Schrader et al., Developmental Opthalmology, Karger 2008, 41, 298-312, each of which is incorporated herein by reference in its entirety). Endpoints in these models may include histopathology of the ocular glands and eye (cornea, etc.) and possibly the classic Schirmer test or modified versions thereof (Barabino et al.) which measure tear production. Activity may be assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists.

Agents may be evaluated in one or more preclinical models of uveitis known to those schooled in the art. These include, but are not limited to, models of experimental autoimmune uveitis (EAU) and endotoxin induced uveitis (EIU). EAU experiements may be performed in the rabbit, rat, or mouse and may involve passive or activate immunization. For instance, any of a number or retinal antigens may be used to sensitize animals to a relevant immunogen after which animals may be challenged ocuarly with the same antigen. The EIU model is more acute and involves local or systemic administration of lipopolysaccaride at sublethal doses. Endpoints for both the EIU and EAU models may include fundoscopic exam, histopathology amongst others. These models are reviewed by Smith et al. (Immunology and Cell Biology 1998, 76, 497-512, which is incorporated herein by reference in its entirety). Activity is assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Some models listed above may also develop scleritis/episcleritis, chorioditis, cyclitis, or iritis and are therefore useful in investigating the potential activity of compounds for the therapeutic treatment of these diseases.

Agents may also be evaluated in one or more preclinical models of conjunctivitis known those schooled in the art. These include, but are not limited to, rodent models utilizing guinea-pig, rat, or mouse. The guinea-pig models include those utilizing active or passive immunization and/or immune challenge protocols with antigens such as ovalbumin or ragweed (reviewed in Groneberg, D.A., et al., Allergy 2003, 58, 1101-1113, which is incorporated herein by reference in its entirety). Rat and mouse models are similar in general design to those in the guinea-pig (also reviewed by Groneberg). Activity may be assessed by dosing via multiple routes of administration (e.g. systemic or topical) which may begin prior to or after measurable disease exists. Endpoints for such studies may include, for example, histological, immunological, biochemical, or molecular analysis of ocular tissues such as the conjunctiva.

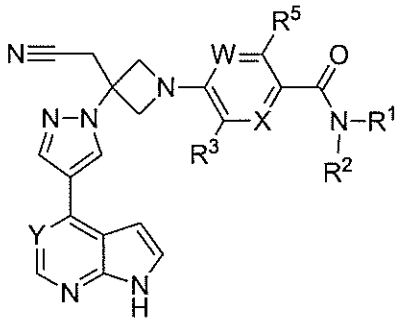
Example G: *In vivo* protection of bone

Compounds may be evaluated in various preclinical models of osteopenia, osteoporosis, or bone resorption known to those schooled in the art. For example, ovariectomized rodents may be used to evaluate the ability of compounds to affect signs and markers of bone remodeling and/or density (W.S.S. Jee and W. Yao, J Musculoskel. Nueron. Interact., 2001, 1(3), 193-207, which is incorporated herein by reference in its entirety). Alternatively, bone density and architecture may be evaluated in control or compound treated rodents in models of therapy (e.g. glucocorticoid) induced osteopenia (Yao, et al. Arthritis and Rheumatism, 2008, 58(6), 3485-3497; and *id.* 58(11), 1674-1686, both of which are incorporated herein by reference in its entirety). In addition, the effects of compounds on bone resorption and density may be evaluable in the rodent models of arthritis discussed above (Example E). Endpoints for all these models may vary but often include histological and radiological assessments as well as immunohisotology and appropriate biochemical markers of bone remodeling.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

The Claims defining the invention are as follows:

1. A compound of Formula I:



I

or a pharmaceutically acceptable salt thereof; wherein:

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl; wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, and 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, $-CF_3$, C_{1-3} alkyl, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -C(O)N(C_{1-3} alkyl)$_2$, -C(O)NH(C_{1-3} alkyl), $-C(O)NH_2$, -C(O)O(C_{1-3} alkyl), -S(O)$_2$(C_{1-3} alkyl), -S(O)$_2$(C_{3-6} cycloalkyl), -C(O)(C_{3-6} cycloalkyl), and -C(O)(C_{1-3} alkyl);

R^2 is H or C_{1-3} alkyl; wherein said C_{1-3} alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, $-CF_3$, NH_2, -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$; or

R^1 and R^2 together with the nitrogen atom to which they are attached form a 4-, 5- or 6-membered heterocycloalkyl ring; which is optionally substituted with 1, 2, or 3 substitutents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, C_{1-3} alkyl, C_{1-3} haloalkyl, $-NH_2$, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, and $-CH_2CN$;

R^3 is H, F, Cl, -CN, C_{1-3} alkyl, $-OCF_3$, $-CF_3$, or -O(C_{1-3} alkyl);

R^4 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^5 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^6 is H, F, Cl, -CN, or C_{1-3} alkyl; and

R^7 is H, F, Cl, -CN, C_{1-3} alkyl, $-CH_2CN$, $-C(O)N(C_{1-3}\text{ alkyl})_2$, $-C(O)NH(C_{1-3}$ alkyl), or $-C(O)NH_2$.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is N.

3. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein Y is CR^7.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^7 is H.

5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein X is N.

6. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein X is CR^4.

7. The compound according to claim 6, or a pharmaceutically acceptable salt thereof, wherein R^4 is H or F.

8. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein W is N.

9. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein W is CR^6.

10. The compound according to claim 9, or a pharmaceutically acceptable salt thereof, wherein R^6 is H, F, or Cl.

11. The compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^5 is H or F.

12. The compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^6 is H or F.

13. The compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^6 is H.

14. The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is H or methyl.

15. The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is H.

16. The compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

17. The compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, $-CF_3$, and methyl.

18. The compound according to any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^1 is isopropyl, ethyl, 1-methylpropyl, 2,2,2-trifluoro-1-methylethyl, 1-cyclopropylethyl, 1-cyclohexylethyl, cyclopropyl, 1-trifluoromethylcyclopropyl, 3,3-difluorocyclobutyl, 1-(1-methylpiperidin-4-yl)ethyl, 1-cyclopropyl-2,2,2-trifluoroethyl, 2,2,2-trifluoroethyl, or 2,2-difluoroethyl.

19. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl; wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, C_{1-3} alkyl, -NH_2, -NH(C_{1-3} alkyl), -N(C_{1-3} alkyl)$_2$, -C(O)N(C_{1-3} alkyl)$_2$, -C(O)NH(C_{1-3} alkyl), -C(O)NH_2, -C(O)O(C_{1-3} alkyl), -S(O)$_2$(C_{1-3} alkyl), -S(O)$_2$(C_{3-6} cycloalkyl), -C(O)(C_{3-6} cycloalkyl), and -C(O)(C_{1-3} alkyl);

R^2 is H or C_{1-3} alkyl; wherein said C_{1-3} alkyl is optionally substituted by 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, NH_2, -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$; or

R^3 is H, F, Cl, -CN, C_{1-3} alkyl, -OCF_3, -CF_3, or -O(C_{1-3} alkyl);

R^4 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^5 is H, F, Cl, -CN, C_{1-3} alkyl, or -O(C_{1-3} alkyl);

R^6 is H, F, Cl, -CN, or C_{1-3} alkyl; and

R^7 is H, F, Cl, -CN, C_{1-3} alkyl, or -CH_2CN.

20. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, -OH, -O(C_{1-3} alkyl), -CN, -CF_3, C_{1-3} alkyl, -NH_2, -NH(C_{1-3} alkyl), and -N(C_{1-3} alkyl)$_2$;

R^2 is H or methyl;

R^3 is H, F, Cl, or methyl;

R^4 is H, F, Cl, or methyl;

R^5 is H, F, Cl, or methyl;

R^6 is H, F, Cl, or methyl; and

R^7 is H.

21. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^4;

W is N or CR^6;

Y is N or CR^7;

R^1 is C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 5-6 membered heterocycloalkyl, or 5-6 membered heterocycloalkyl-C_{1-3} alkyl, wherein said C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl-C_{1-3} alkyl, 4-6 membered heterocycloalkyl, or 4-6 membered heterocycloalkyl-C_{1-3} alkyl are each optionally substituted with 1, 2, or 3 substituents independently selected from fluoro, $-CF_3$, and methyl;

R^2 is H or methyl;

R^3 is H, F, or Cl;

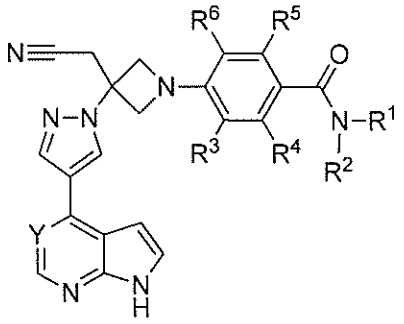
R^4 is H or F;

R^5 is H or F;

R^6 is H; and

R^7 is H.

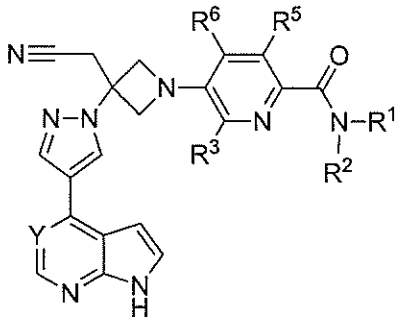
22. The compound according to any one of claims 1 to 4, 7, and 10 to 21, having Formula II:



II

or a pharmaceutically acceptable salt thereof.

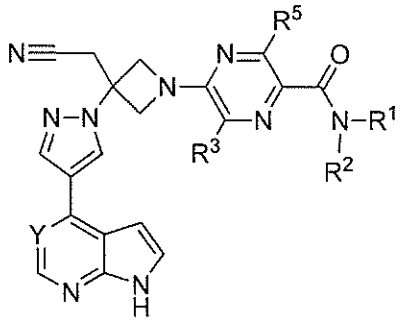
23. The compound according to any one of claims 1 to 4 and 10 to 21, having Formula III:



III

or a pharmaceutically acceptable salt thereof.

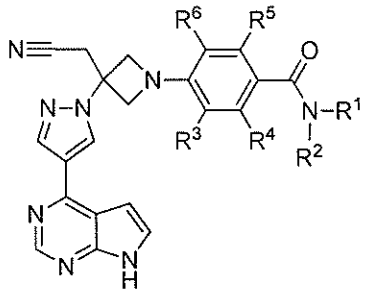
24. The compound according to any one of claims 1 to 4 and 11 to 21, having Formula IV:



IV

or a pharmaceutically acceptable salt thereof.

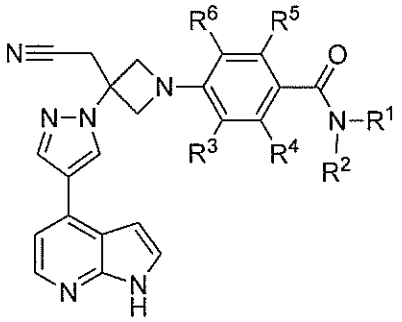
25. The compound according to any one of claims 1, 7, and 10 to 21, having Formula IIa:



IIa

or a pharmaceutically acceptable salt thereof.

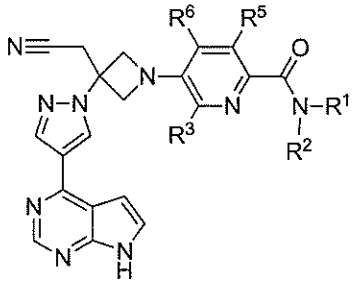
26. The compound according to any one of claims 1, 7, and 10 to 21, having Formula IIb:



IIb

or a pharmaceutically acceptable salt thereof.

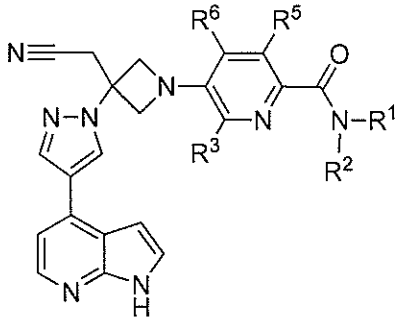
27. The compound according to any one of claims 1 and 10 to 21, having Formula IIIa:



IIIa

or a pharmaceutically acceptable salt thereof.

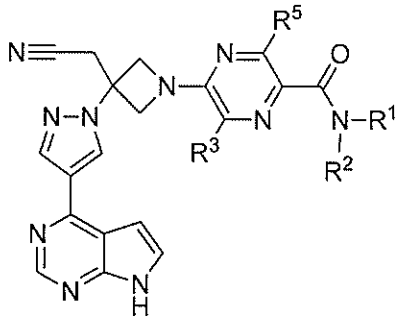
28. The compound according to any one of claims 1 and 10 to 21, having Formula IIIb:



IIIb

or a pharmaceutically acceptable salt thereof.

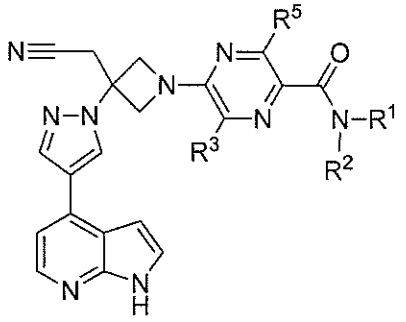
29. The compound according to any one of claims 1 and 11 to 21, having Formula IVa:



IVa

or a pharmaceutically acceptable salt thereof.

30. The compound according to any one of claims 1 and 11 to 21, having Formula IVb:



IVb

or a pharmaceutically acceptable salt thereof.

31. The compound according to claim 1, selected from:

4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-3-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]-3-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-cyclopropyl-3-fluoro-N-methylbenzamide;

5-Chloro-4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-N-isopropylbenzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(3,3-difluorocyclobutyl)pyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-*N*-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclohexylethyl]-2-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(1-methylpiperidin-4-yl)ethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-

pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2,5-difluorobenzamide;

5-Chloro-4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2-fluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-2-fluoro-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-1-yl}-N-[(1*R*)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-ethylpyridine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-methylpropyl]benzamide; and

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoro-1-methylethyl)benzamide;

or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 1, selected from:

4-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-3-fluoro-N-isopropylbenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylpyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-2,2,2-trifluoro-1-methylethyl]pyrazine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoroethyl)pyrazine-2-carboxamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2-difluoroethyl)-2,5-difluorobenzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]benzamide;

4-{3-(Cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1R)-1-cyclopropylethyl]-2-fluorobenzamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[1-(trifluoromethyl)cyclopropyl]pyridine-2-carboxamide;

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropylethyl]pyrazine-2-carboxamide; and

5-{3-(Cyanomethyl)-3-[4-(1H-pyrrolo[2,3-b]pyridin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]pyrazine-2-carboxamide;

or a pharmaceutically acceptable salt thereof.

33. A compound, which is 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-isopropylbenzamide, or a pharmaceutically acceptable salt thereof.

34. A compound, which is 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-N-(2,2,2-trifluoro-1-methylethyl)benzamide, or a pharmaceutically acceptable salt thereof.

35. A compound, which is 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1S)-2,2,2-trifluoro-1-methylethyl]benzamide, or a pharmaceutically acceptable salt thereof.

36. The compound according to claim 1, which is 4-{3-(cyanomethyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-1-yl}-2,5-difluoro-N-[(1R)-2,2,2-trifluoro-1-methylethyl]benzamide, or a pharmaceutically acceptable salt thereof.

37. A composition comprising a compound according to any one of Claims 1 to 36, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

38. Use of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof for preparation of a medicament for inhibiting an activity of JAK1.

39. The use according to claim 38, wherein said compound, or pharmaceutically acceptable salt thereof, is selective for JAK1 over JAK2.

40. Use of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment of an autoimmune disease, a cancer, a myeloproliferative disorder, an inflammatory disease, a bone resorption disease, or organ transplant rejection in a patient in need thereof.

41. The use according to claim 40, wherein said autoimmune disease is a skin disorder, multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, type I diabetes, lupus, inflammatory bowel disease, Crohn’s disease,

myasthenia gravis, immunoglobulin nephropathies, myocarditis, or autoimmune thyroid disorder.

42. The use according to claim 40, wherein said autoimmune disease is rheumatoid arthritis.

43. The use according to claim 40, wherein said autoimmune disease is a skin disorder.

44. The use according to claim 43, wherein said skin disorder is atopic dermatitis, psoriasis, skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.

45. The use according to claim 40, wherein said cancer is a solid tumor.

46. The use according to claim 40, wherein said cancer is prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid cancer, Kaposi's sarcoma, Castleman's disease or pancreatic cancer.

47. The use according to claim 40, wherein said cancer is lymphoma, leukemia, or multiple myeloma.

48. The use according to claim 40, wherein said myeloproliferative disorder is polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML), hypereosinophilic syndrome (HES), idiopathic myelofibrosis (IMF), or systemic mast cell disease (SMCD).

49. The use according to claim 40, wherein said myeloproliferative disorder is myelofibrosis.

50. The use according to claim 40, wherein said myeloproliferative disorder is primary myelofibrosis (PMF).

51. The use according to claim 40, wherein said myeloproliferative disorder is post polycythemia vera myelofibrosis (Post-PV MF).

52. The use according to claim 40, wherein said myeloproliferative disorder is post-essential thrombocythemia myelofibrosis (Post-ET MF).

53. The use according to claim 40, wherein said bone resorption disease is osteoporosis, osteoarthritis, bone resorption associated with hormonal imbalance, bone resorption associated with hormonal therapy, bone resorption associated with autoimmune disease, or bone resorption associated with cancer.